FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER

Rec'd PCT/PTO 01 MAR 2002

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

10/070084

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/08487	**31 August 2000**	**4 September 1999**

TITLE OF INVENTION

Benzophenones As Inhibitors Of Reverse Transcriptase

APPLICANT(S) FOR DO/EO/US

ANDREWS, CW; CHAN, JH; FREEMAN, GA; ROMINES, KR; TIDWELL, JH

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

   a) Request
   b) PCT/IB306 (2)
   c) Correction to PCT request before expiration of 30th month (sent 18 February 2002)

10/070084 Rec'd PCT/PTO 01 MAR 2002

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/070084	PCT/EP00/08487	PU3517USW

24. The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1040.00		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $890.00		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $740.00		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $710.00		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	51 - 20 =	31	x $18.00	$558.00	
Independent claims	11 - 3 =	8	x $84.00	$672.00	
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00	

TOTAL OF ABOVE CALCULATIONS =	$2,120.00	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.	$0.00	
SUBTOTAL =	$2,120.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +	$0.00	
TOTAL NATIONAL FEE =	$2,120.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐	$0.00	
TOTAL FEES ENCLOSED =	$2,120.00	
	Amount to be: refunded	$
	charged	$

a. ☐ A check in the amount of ______________ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 07-1392 in the amount of $2,120.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 07-1392 A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

23347

PATENT TRADEMARK OFFICE

Karen R. Prus

SIGNATURE

Karen Prus

NAME

39,337

REGISTRATION NUMBER

March 1, 2002

DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Andrews, CW

International Application No.: PCT/EP00/08487

International Filing Date: August 31, 2000

Title: Benzophenones as Inhibitors of Reverse Transcriptase

Commissioner for Patents
Washington, D.C. 20231

Attention: Box PCT/DO/EO/US

FIRST PRELIMINARY AMENDMENT

Sir:

The above identified application is being transmitted herewith for entry into the U.S. National Phase under Chapter II of the PCT. For the purposes of adding the priority information and amending the application to conform to US Rules, please amend the application as follows:

In the Abstract:

Please substitute the attached Abstract, which has been placed on a separate piece of paper according to US practice.

In the Specification:

On the first line of the specification, after the Title, please add:

--This application is filed pursuant to 35 U.S.C. § 371 as a United States National Phase Application of International Application No. PCT/EP00/08487 filed August 31, 2000, which claims priority from GB 9920872.0 filed September 4, 1999 --

In the Claims:

Please cancel claims 31, 32, 33, and 37.

Please amend the claims as follows:

14. (Amended) A compound according to claim 6 wherein X is O.

20. (Amended) A compound according to claim 4 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

26. (Amended) A compound according to claim 4 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

27. (Amended) A method of treatment of a viral infection in a mammal comprising administering to said mammal an antivirally effective amount of a compound according to claim 2.

29. (Amended) A method of inhibiting HIV reverse transcrptase comprising administering to a mammal an effective amount of a compound according to claim 2.

30. (Amended) A method of preventing HIV infection, or of treating HIV infection, comprising administering to a mammal an effective amount of a compound according to claim 2.

34. (Amended) A pharmaceutical composition comprising an effective amount of a compound according to claim 2 together with a pharmaceutically acceptable carrier.

Please add the following new claims:

38. A compound according to claim 6 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally

substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

39. A compound according to claim 7 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

40. A compound according to claim 17 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

41. A compound according to claim 18 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the

para position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

42. A compound according to claim 19 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino,

heterocycleC_{1-8}alkyl, -C(O)NH_2, -S(O)R^7, -S(O)$_2R^7$, -C(O)R^7, -NS(O)$_2R^7$, -S(O)$_2NR^8R^9$, -S(O)$_2NHR^{11}$, -SO_2R^{11}, -OR^{11} , -C(O)R^{11}, -C(O)NR^{11}, -C(O)OR^{11}, -NR^{11}, -NC(O)R^{11}, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and C(O)OR^{11}, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with -C(O)R^{11};

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, -NO_2, -NH_2, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, -S(O)$_2NR^8R^9$, -NR^8R^9, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

43. A compound according to claim 6 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

44. A compound according to claim 7 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

45. A compound according to claim 17 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

46. A compound according to claim 18 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

47. A compound according to claim 19 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

48. A method of treatment of a viral infection in a mammal comprising administering to said mammal an antivirally effective amount of a compound according to claim 4.

49. A method of treatment of a viral infection in a mammal comprising administering to said mammal an antivirally effective amount of a compound according to claim 23.

50. A method of inhibiting HIV reverse transcrptase comprising administering to a mammal an effective amount of a compound according to claim 4.

51. A method of inhibiting HIV reverse transcrptase comprising administering to a mammal an effective amount of a compound according to claim 23.

52. A method of preventing HIV infection, or of treating HIV infection, comprising administering to a mammal an effective amount of a compound according to claim 4.

53. A method of preventing HIV infection, or of treating HIV infection, comprising administering to a mammal an effective amount of a compound according to claim 23.

54. A pharmaceutical composition comprising an effective amount of a compound according to claim 4 together with a pharmaceutically acceptable carrier.

55. A pharmaceutical composition comprising an effective amount of a compound according to claim 23 together with a pharmaceutically acceptable carrier.

REMARKS

Applicants have attached an abstract on a separate sheet of paper as required by US practice. Applicants have amended the specification for purposes of adding the priority information. Claims 31, 32, 33, and 37 have been cancelled. Claims 14, 20, 26, 27, 29, 30, and 34 have been amended to remove the multiple dependencies and new claims 38-55 have been added instead in accordance with U.S. practice. No new matter has been added. Applicants respectfully submit that the instant application is ready for examination on the merits. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted,

Karen L. Prus

Karen L. Prus
Attorney for Applicants
Registration No. 39,337

Date: March 1, 2002

GlaxoSmithKline Inc.
Corporate Intellectual Property
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709
Phone: 919-483-2192
Facsimile: 919-483-7988

Copy of the Claims with Markings to Show Changes Made

14. (Amended) A compound according to [any of claims 1, 5, 6, 8, 10, or 12] claim 6 wherein X is O.

20. (Amended) A compound according to [any of claims 1, 3, 4, 5, 6, 7, 17, 18, or 1] claim 4 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

26. (Amended) A compound according to [any of claims 1, 3, 4, 5, 6, 7, 17, 18, or 19] claim 4 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

27. (Amended) A method of treatment of a viral infection in a mammal comprising administering to said mammal an antivirally effective amount of a compound according to [any of claims 1 to 26] claim 2.

29. (Amended) A method of inhibiting HIV reverse transcrptase comprising administering to a mammal an effective amount of a compound according to [any of claims 1 to 26] claim 2.

30. (Amended) A method of preventing HIV infection, or of treating HIV infection, comprising administering to a mammal an effective amount of a compound according to [any of claims 1 to 26] claim 2.

31. (Cancelled)

32. (Cancelled)

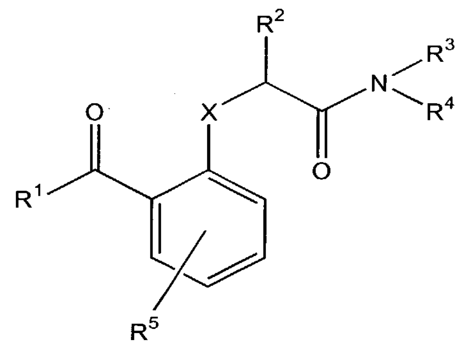
33. (Canceled)

34. (Amended) A pharmaceutical composition comprising an effective amount of a compound according to [any of claims 1 to 26] claim 2 together with a pharmaceutically acceptable carrier.

37. (Cancelled).

Clean Copy of the Claims

1. A compound of formula (I



(I)

wherein:

X is C, O, or N;

R^1 is C_{1-8}alkyl; C_{3-6}cycloalkyl; C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl,

C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$, $-S(O)_2NR^8R^9$, and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-S(O)_2R^{11}$, $-S(O)_2NR^7COR^{11}$, $-S(O)_2NHCOR^{11}$, $-S(O)_2[COR^{11}]_n$ wherein n is 1, 2, or 3, $-OR^{11}$, $-OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_3_6cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, alkoxy, $-S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, and C_{1-8}alkyl; heterocycle optionally substituted with heterocycleC_{1-8}alkyl; or C_{6-14}aryl optionally substituted with alkoxy;

R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;
or a pharmaceutically acceptable derivative thereof,
provided that

(a) when X is N; R^1 is C_{6-14}aryl substituted with halogen; R^2 and R^3 are hydrogen; R^5 is halogen; R^4 cannot be heterocycle substituted with C_{1-8}alkyl;

(b) when X is C; R^2 is hydrogen, halogen or C_{1-8}alkyl; R^3 is hydrogen; R^4 is C_{6-14}aryl substituted with halogen, hydroxy, or C_{1-8}alkyl; R^5 is hydrogen, halogen, C_{1-8}alkyl, or alkoxy; then R^1 cannot be C_{1-8}alkyl, C_{3-6}cylcoalkyl, or C_{6-14}aryl substituted with halogen, C_{1-8}alkyl, alkoxy, or C_{6-14}arylC_{2-6}alkenyl; and

(c) when X is C; R^2 is hydrogen or alkyl, R^3 is hydrogen, R^4 is C_{6-14}aryl substituted with halogen, CN, C_{1-8}alkyl, or $-NO_2$; R^5 is hydrogen, $-NO_2$ or NH_2, then R^1 cannot be C_{10-14} aryl substituted with alkoxy.

2. A compound of formula (I) according to claim 1 wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, -CN, $-SR^6$, $-S(O)_2R^6$; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, and C_{6-14}arylC_{1-8}alkyl; R^6 is C_{1-8}alkyl, optionally substituted with halogen; R^7 is C_{1-8} alkyl optionally substituted with one or more substituents selected from the group consisting of hydroxy; $-NH_2$, or heterocycle; R^2 is hydrogen; R^3 is hydrogen or C_{1-8} alkyl; R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$, $S(O)_2NR^8R^9$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, and heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl and heterocycleC_{1-8}alkyl; $R^8$and R^9 are the same or different and are selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cycloalkyl; R^{10} is C_{1-8}alkyl; R^{11} is C_{1-8}alkyl, optionally substituted with $-SO_2NR^8R^9$; and R^5 is halogen or $-NO_2$; or a pharmaceutically acceptable derivative thereof.

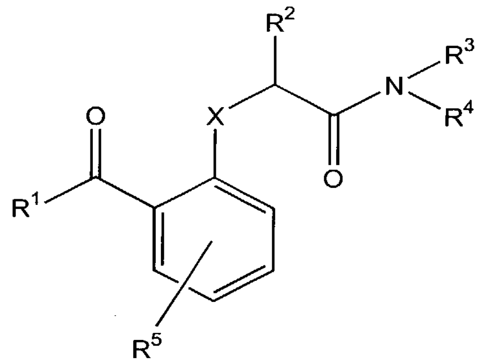
3. A compound of formula (I) according to claim 1 wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of

halogen, $-CF_3$, C_{1-8}alkyl, and -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, $-NO_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-NS(O)_2R^7$, wherein R^7 is $-NH_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

4. A compound of formula (I) according to claim 1 wherein X is O; R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, CF_3, -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $S(O)_2NR^8R^9$, wherein $R^8$and R^9 are independently selected from the group consisting of hydrogen, C_3-6cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl.

5. A compound of formula (I) according to claim 1 wherein R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, and -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, $-NO_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-NS(O)_2R^7$, wherein R^7 is $-NH_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof provided that when X is C; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with halogen, CN, C_{1-8}alkyl, $-NO_2$; and R^5 is halogen, then R^1 cannot be C_{6-10}aryl substituted with alkoxy.

6. A compound of formula (IA)



(IA)

wherein:

X is C, O, or N;

R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-}

$_8$alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-S(O)_2R^{11}$, $-S(O)_2NR^7COR^{11}$, $-S(O)_2NHCOR^{11}$, $-S(O)_2[COR^{11}]_n$ wherein n is 1, 2, or 3, $-OR^{11}$, $-OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_3-6cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, alkoxy, $-S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, and C_{1-8}alkyl; heterocycle optionally substituted with heterocycleC_{1-8}alkyl; or C_{6-14}aryl optionally substituted with alkoxy;

R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

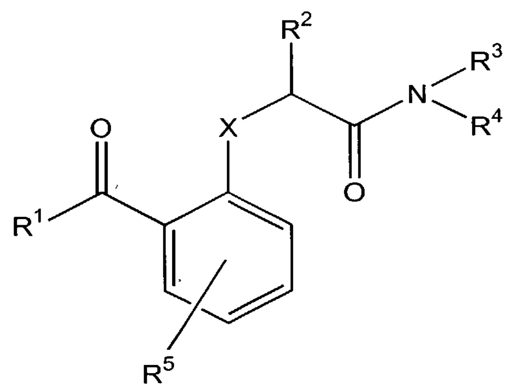
or a pharmaceutically acceptable derivative thereof provided that

a) when X is C; R^2 is hydrogen, halogen or C_{1-8}alkyl; R^3 is hydrogen; R^4 is C_{6-14}aryl substituted with halogen, hydroxy, or C_{1-8}alkyl; R^5 is hydrogen, halogen, C_{1-8}alkyl, or alkoxy; then R^1 cannot be C_{1-8}alkyl, C_{3-6}cycloalkyl, or C_{6-14}aryl substituted with halogen, C_{1-8}alkyl, or C_{6-14}arylC_{2-6}alkenyl; and

(b) when X is C; R^2 is hydrogen or alkyl; R^3 is hydrogen; R^4 is C_{6-14}aryl substituted with halogen, CN, alkyl, or $-NO_2$; R^5 is hydrogen, $-NO_2$, or NH_2, then R^1 cannot be C_{10-14} aryl substituted with alkoxy.

7. A compound of formula (IA) according to claim 6 wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, -CN, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, $-S(O)_2R^7$, $-S(O)_2NR^8R^9$, -OR^{11} , heterocycleC_{2-6}alkenyl, and heterocycle which may be optionally substituted with oxo; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

8. A compound of compounds of formula (IB)



(IB)

wherein:

X is C, O, or N;

R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and

C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$, $-SR^{10}N(R^{10})_2$ and $-S(O)_2NR^8R^9$;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_3_6cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

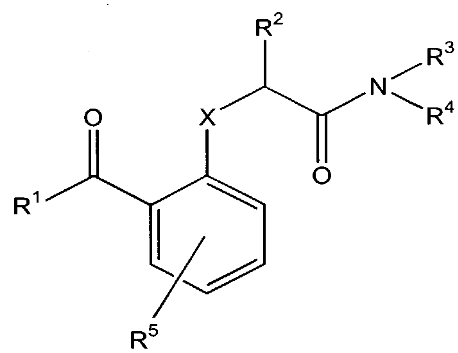
R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, alkoxy, $-S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, and C_{1-8}alkyl; heterocycle optionally substituted with heterocycleC_{1-8}alkyl; or C_{6-14}aryl optionally substituted with alkoxy;

R^5 is hydrogen, halogen,C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof provided that when X is N; R^1 is C_{6-14}aryl substituted with halogen; R^2 and R^3 are hydrogen; R^5 is halogen; R^4 cannot be heterocycle substituted with C_{1-8}alkyl.

9. A compound of formula (IB) according to claim 8 wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, and -CN; R^2 is hydrogen; R^3 is hydrogen; R^4 is heterocycle; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

10. A compound of formula (IC)



(IC)

wherein:

X is C, O, or N;

R^1 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, halogen, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-S(O)_2R^{11}$, $-S(O)_2NR^7COR^{11}$, $-S(O)_2NHCOR^{11}$, $-S(O)_2[COR^{11}]_n$ wherein n is 1, 2, or 3, $-OR^{11}$, $-OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from

the group consisting of -CN and heterocycle, optionally substituted with -$C(O)R^{11}$;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; -NH_2; or heterocycle;

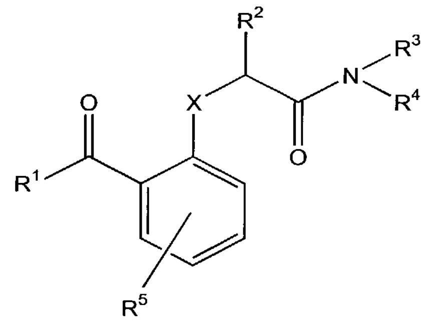
$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_3.6cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, alkoxy, -$S(O)_2NR^8R^9$, -NR^8R^9, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen, halogen, C_{1-8}alkyl, -NO_2, -NH_2, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

11. A compound of formula (IC) according to claim 10 wherein X is O; R^1 is heterocycle, optionally substituted with -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -$S(O)_2NR^8R^9$, -OR^{11} , and heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

12. A compound of formula (ID):



(ID)

wherein:

X is C, O, or N;

R^1 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, halogen, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$, $-S(O)_2NR^8R^9$, and $-SR^{10}N(R^{10})_2$; or R^3 and R^4 together with the nitrogen atom to which they are attached form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_3_6cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{10} is C_{1-8}alkyl;

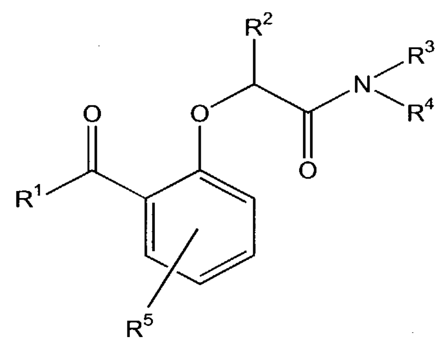
R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, and C_{1-8}alkyl;

R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

13. A compound of formula (ID) according to claim 12 wherein X is O; R^1 is heterocycle; R^2 and R^3 are hydrogen; R^4 is heterocycle; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

14. A compound according to claim 6 wherein X is O.

15. A compound of formula (II):



(II)

wherein:

R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy,

halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 and R^4 form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$;

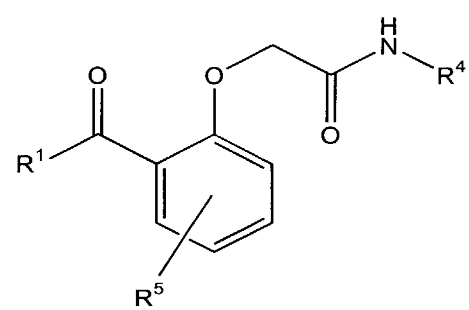
provided that when R^1 is unsubstituted C_{6-14}aryl, then R^3R^4 is substituted.

R^5 is hydrogen, halogen,C_{1-8}alkyl, $-NO_2$, $-NH_2$,C_{1-8}alkylamino, CF_3, or alkoxy;

or a pharmaceutically acceptable derivative thereof.

16. A compound of formula (II) according to claim 15 wherein R^1 is C_{6-14}aryl which is substituted with halogen; R^2 is hydrogen; R^3 and R^4 form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

17. A compound of formula (III):



(III)

wherein:

R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-S(O)_2NHR^{11}$, $S(O)_2R^{11}$, $OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $-C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

$R^8$and R^9 are independently selected from the group consisting of hydrogen; C_3-6cycloalkyl; C_{1-8}alkyl optionally substituted with one or more substituents

selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl; or $-C(O)NH_2$;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, alkoxy, $-S(O)_2NR^8R^9$, $-NR^8R^9$ and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen; halogen; C_{1-8}alkyl; $-NO_2$; $-NH_2$; C_{1-8}alkylamino; CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof,
provided that:

(a) when R^4 is C_{6-14}aryl substituted with OR^{11} wherein R^{11} is NR^8R^9 wherein R^8 and R^9 are C_{1-8}alkyl, and R^1 is C_{6-14}aryl, then R^1 cannot be substituted in the para position, and

(b) R^1 and R^4 cannot both be unsubstituted.

18. A compound of formula (III) according to claim 17 wherein R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, -CN, $-SR^6$, $-S(O)_2R^6$; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, and C_{6-14}arylC_{1-8}alkyl; R^6 is C_{1-8}alkyl, optionally substituted with halogen; R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, $-NH_2$, or heterocycle; R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, $-C(O)NH_2$, $-S(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; $R^8$and R^9 are the same or different and are selected from the group consisting of hydrogen, C_{1-8}alkyl,

C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cycloalkyl; R^{10} is C_{1-8}alkyl; R^{11} is C_{1-8}alkyl, optionally substituted with $-S(O)_2NR^8R^9$; and R^5 is halogen or $-NO_2$; or a pharmaceutically acceptable derivative thereof.

19. A compound of formula (III) according to claim 17 wherein R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, and -CN; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, $-NO_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-NS(O)_2R^7$, wherein R^7 is $-NH_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

20. A compound according to claim 4 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

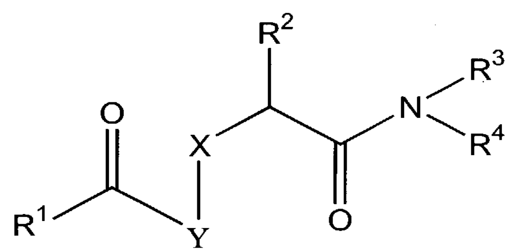
R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted

with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

21. A compound of formula (IV)



(IV)

wherein:

X is C, O, or N;

Y is heterocycle optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, $-CF_3$, or alkoxy;

R^1 is C_{1-8}alkyl; C_{3-6}cycloalkyl; C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; or heterocycle, optionally

substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen,or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, OR^{11} and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NSO_2R^7$, -$S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cycloalkyl;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-SO_2NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen, halogen,C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

or a pharmaceutically acceptable derivative thereof.

22. A compound of formula (IV) according to claim 21 wherein Y is a heterocycle substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -NO_2, -NH_2, C_{1-8}alkylamino, -CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof. More preferred compounds of formula (IV) are compounds wherein X is O. Most preferred compounds of formula (IV) are those wherein X is O and Y is a heterocycle substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -NO_2, -NH_2, C_{1-8}alkylamino, -CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

23. A compound selected from the group consisting of:

2-[2-(1-benzothiophen-2-ylcarbonyl)-4-chlorophenoxy]-N-phenylacetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1H-imidazol-1-yl)phenyl]acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1H-1,2,4-triazol-1-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(4-morpholinyl)phenyl]acetamide;

N-[4-(aminosulfonyl)phenyl]-2-(2-benzoyl-4-chlorophenoxy)acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[(1,3-thiazol-2-ylamino)sulfonyl]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(4-methyl-1-piperazinyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(hydroxymethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[(methylamino)sulfonyl]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1,1-dioxo-1lambda~6~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(4-morpholinyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[3-(dimethylamino)propoxy]-2-methylphenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-5-yl)acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(4-morpholinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[3-(1H-imidazol-1-yl)propoxy]-2-methylphenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-{2-methyl-4-[3-(4-morpholinyl)propoxy]phenyl}acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-oxo-1lambda~4~,4-thiazinan-4-yl)propoxy]phenyl}acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(2-benzoyl-4-chlorophenoxy)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]acetamide;

2-[2-(1-benzofuran-2-ylcarbonyl)-4-chlorophenoxy]-N-phenylacetamide

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-phenylacetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(2-furoyl)phenoxy]acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-(1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3-furoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-{4-chloro-2-[(1-methyl-1H-pyrrol-2-yl)carbonyl]phenoxy}-N-phenylacetamide;

2-(4-chloro-2-{[5-(2-pyridinyl)-2-thienyl]carbonyl}phenoxy)-N-phenylacetamide;

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-pyridinylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(2-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(4-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[2-(2-bromobenzoyl)-4-chlorophenoxy]acetamide;

2-{4-chloro-2-[(5-methyl-3-isoxazolyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]acetamide;

2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}acetamide;

2-{4-chloro-2-[3-(trifluoromethyl)benzoyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(3-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[2-(3-bromobenzoyl)-4-chlorophenoxy]acetamide;

2-[4-chloro-2-(3-methylbenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-pyridinylcarbonyl)phenoxy]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(1-methyl-1H-imidazol-2-yl)carbonyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide

N-(1,3-benzothiazol-6-yl)-2-(2-benzoyl-4-chlorophenoxy)acetamide

2-(4-chloro-2-{3-[(trifluoromethyl)sulfanyl]benzoyl}phenoxy)-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide

2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

N-(1,3-benzothiazol-6-yl)-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-(2-methyl-1,3-benzothiazol-5-yl)acetamide

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(4-chloro-2-{3-[(trifluoromethyl)sulfanyl]benzoyl}phenoxy)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(methylsulfonyl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-(2-cyclopentylethynyl)benzoyl]phenoxy}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-(2-phenylethynyl)benzoyl]phenoxy}acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

N-(1,2-benzisothiazol-5-yl)-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-1-(2,3-dihydro-1H-indol-1-yl)-1-ethanone;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

N-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide;

2-{2-[3,5-bis(trifluoromethyl)benzoyl]-4-chlorophenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{2-[(5-bromo-3-pyridinyl)carbonyl]-4-chlorophenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(6-methyl-1,3-benzothiazol-5-yl)acetamide;

N-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(4-chloro-2-{3-[(trifluoromethyl)sulfonyl]benzoyl}phenoxy)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[4-(1,3-thiazol-2-yl)phenyl]acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[4-(1,3-oxazol-2-yl)phenyl]acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-{4-[(3-hydroxypropyl)sulfonyl]-2-methylphenyl}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(2-methyl-4-{3-[(methylamino)sulfonyl]propoxy}phenyl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(4-{3-[(dimethylamino)sulfonyl]propoxy}-2-methylphenyl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{2-[(5-bromo-3-pyridinyl)carbonyl]-4-chlorophenoxy}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-{4-[3-(1H-imidazol-1-yl)propoxy]-2-methylphenyl}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-{2-methyl-4-[(E)-4-(1-pyrrolidinyl)-1-butenyl]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[6-(aminosulfonyl)-4-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dimethylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-ethylbenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]-*N*-{4-[3-(2,5-dihydro-1*H*-pyrrol-1-yl)propoxy]-2-methylphenyl}acetamide hydrochloride;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(6-cyano-2-pyridinyl)carbonyl]phenoxy}acetamide;

N-[6-(aminosulfonyl)-2-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dicyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-cyano-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

and pharmaceutically acceptable derivatives thereof.

24. A compound selected from the group consisting of compound number 7, 32, 33, 36, 38, 44, 45, 49, 51, 52, 61, 65, 66, 71, 75, 76, 111, 112, 115, 118, 119, 128, 129, 171, 172, 191, 192, 199, 200, 206, 207, 224, 225, 232, 233, 235, 236, 246, 247, 253, 254, 255, 256, 259, 260, 261, 262, 264, 265, 267, 268, 288, 289, 290, 409, 412, 428, 430, 431, 433, 491, 564, 587, 475, 478, 498, 593, 483, 637, 503, 601, 658 and pharmaceutically acceptable derivatives thereof.

25. A compound selected from the group consisting of:

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-fluoro-5-(trifluoromethyl)benzoyl]acetamide;

N-{4-[3-(aminosulfonyl)propoxy] -2-methylphenyl}-2-{4-chloro-2-[3-fluoro-5-(trifluomethyl)benzoyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-fluorobenzoyl)phenoxy]acetamide;
N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;
N-[6-(aminosulfonyl)-4-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;
N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-cyanobenzoyl)phenoxy]acetamide;
N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dimethylbenzoyl)phenoxy]acetamide;
N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-ethylbenzoyl)phenoxy]acetamide;
2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]-*N*-{4-[3-(2,5-dihydro-1*H*-pyrrol-1-yl)propoxy]-2-methylphenyl}acetamide hydrochloride;
N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-methylbenzoyl)phenoxy]acetamide;
N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;
N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(6-cyano-2-pyridinyl)carbonyl]phenoxy}acetamide;
N-[6-(aminosulfonyl)-2-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;
N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dicyanobenzoyl)phenoxy]acetamide;
and pharmaceutically acceptable derivatives thereof.

26. A compound according to claim 4 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

27. A method of treatment of a viral infection in a mammal comprising administering to said mammal an antivirally effective amount of a compound according to claim 2.

28. The method according to claim 27 wherein the viral infection is an HIV infection.

29. A method of inhibiting HIV reverse transcrptase comprising administering to a mammal an effective amount of a compound according to any of claim 2.

30. A method of preventing HIV infection, or of treating HIV infection, comprising administering to a mammal an effective amount of a compound according to claim 2.

34. A pharmaceutical composition comprising an effective amount of a compound according to claim 2 together with a pharmaceutically acceptable carrier.

35. A pharmaceutical composition according to claim 34 in the form of a tablet or capsule.

36. A pharmaceutical composition according to claim 34 in the form of a liquid.

38. A compound according to claim 6 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, -$S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino,

heterocycleC_{1-8}alkyl, -C(O)NH_2, -S(O)R^7, -S(O)$_2R^7$, -C(O)R^7, -NS(O)$_2R^7$, -S(O)$_2NR^8R^9$, -S(O)$_2NHR^{11}$, -SO_2R^{11}, -OR^{11} , -C(O)R^{11}, -C(O)NR^{11}, -C(O)OR^{11}, -NR^{11}, -NC(O)R^{11}, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and C(O)OR^{11}, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with -C(O)R^{11};

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, -NO_2, -NH_2, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, -S(O)$_2NR^8R^9$, -NR^8R^9, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

39. A compound according to claim 7 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, -CF_3, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, -NO_2, -NH_2, -SR^6, -S(O)$_2R^6$, -S(O)R^7, -S(O)$_2R^7$, -C(O)R^7, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, -CF_3, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, -CF_3, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, -NO_2, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, -C(O)NH_2, -S(O)R^7, -S(O)$_2R^7$, -C(O)R^7, -NS(O)$_2R^7$, -S(O)$_2NR^8R^9$, -S(O)$_2NHR^{11}$, -SO_2R^{11}, -OR^{11} , -C(O)R^{11}, -C(O)NR^{11}, -C(O)OR^{11}, -

NR^{11}, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

40. A compound according to claim 17 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of

oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

41. A compound according to claim 18 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted

with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

42. A compound according to claim 19 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;
R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

43. A compound according to claim 6 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

44. (Amended) A compound according to claim 7 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

45. A compound according to claim 17 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

46. A compound according to claim 18 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

47. A compound according to claim 19 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

48. A method of treatment of a viral infection in a mammal comprising administering to said mammal an antivirally effective amount of a compound according to claim 4.

49. A method of treatment of a viral infection in a mammal comprising administering to said mammal an antivirally effective amount of a compound according to claim 23.

50. A method of inhibiting HIV reverse transcrptase comprising administering to a mammal an effective amount of a compound according to claim 4.

51. A method of inhibiting HIV reverse transcrptase comprising administering to a mammal an effective amount of a compound according to claim 23.

52. A method of preventing HIV infection, or of treating HIV infection, comprising administering to a mammal an effective amount of a compound according to claim 4.

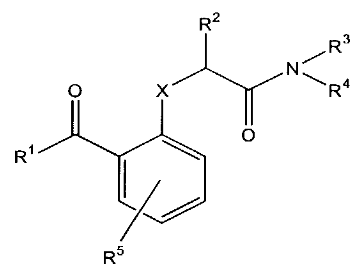
53. A method of preventing HIV infection, or of treating HIV infection, comprising administering to a mammal an effective amount of a compound according to claim 23.

54. A pharmaceutical composition comprising an effective amount of a compound according to claim 4 together with a pharmaceutically acceptable carrier.

55. A pharmaceutical composition comprising an effective amount of a compound according to claim 23 together with a pharmaceutically acceptable carrier.

ABSTRACT

The present invention includes benzophenone compounds (I)



(I)

which are useful in the treatment of HIV infections.

Benzophenones As Inhibitors of Reverse Transcriptase

Background of the Invention

The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS"), a disease characterized by the destruction of the immune system, particularly of $CD4^+$ T-cells, with attendant susceptibility to opportunistic infections, and its precursor AIDS-related complex ("ARC"), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss. HIV is a retrovirus; the conversion of its RNA to DNA is accomplished through the action of the enzyme reverse transcriptase. Compounds that inhibit the function of reverse transcriptase inhibit replication of HIV in infected cells. Such compounds are useful in the prevention or treatment of HIV infection in humans.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs), in addition to the nucleoside reverse transcriptase inhibitors gained a definitive place in the treatment of HIV-1 infections. The NNRTIs interact with a specific site of HIV-1 reverse transcriptase that is closely associated with, but distinct from, the NRTI binding site. NNRTIs, however, are notorious for rapidly eliciting resistance due to mutations of the amino acids surrounding the NNRTI-binding site (E. De Clercq, *Il Famaco* 54, 26-45, 1999). Failure of long-term efficacy of NNRTIs is often associated with the emergence of drug-resistant virus strains (J. Balzarini, *Biochemical Pharmacology*, Vol 58, 1-27, 1999). Moreover, the mutations that appear in the reverse transcriptase enzyme frequently result in a decreased sensitivity to other reverse transcriptase inhibitors, which results in cross-resistance.

JP 59181246 disclosed certain benzophenones useful as anticancer agents. Certain benzophenone derivatives as inhibitors of HIV-1 reverse transriptase were disclosed in Wyatt et al. (J. Med. Chem. 38:1657-1665, 1995). However, these compounds were primarily active against wild-type HIV-1 reverse transcriptase, rapidly induced resistant virus, and were inactive against a common resistant strain.

We have now discovered that the compounds of the present invention are useful as inhibitors of both wild type and mutant variants of HIV reverse transcriptase.

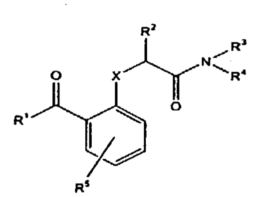
Brief Description of the Invention

A first aspect of the invention features compounds of formula I, IA, IB, IC, ID, II, III, and IV. These compounds are useful in the inhibition of HIV reverse transcriptase, particularly its resistant varieties, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS and/or ARC, either as compounds, pharmaceutically acceptable salts or pharmaceutical composition ingredients. A second aspect of the invention features methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV as monotherapy or in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. A third aspect of the invention features pharmaceutical compositions comprising the above-mentioned compounds and which are suitable for the prevention or treatment of HIV infection. A fourth aspect of the invention features processes for making the above-mentioned compounds.

Detailed Description of the Invention

The present invention relates to compounds of formula I, IA, IB, IC, ID, II, III, IV and combinations thereof, or pharmaceutically acceptable salts thereof, in the inhibition of HIV reverse transcriptase and its resistant varieties, the prevention or treatment of infection by HIV and in the treatment of the resulting acquired immune deficiency syndrome (AIDS).

The present invention features compounds of formula (I)



(I)

wherein:

X is C, O, or N;

R^1 is C_{1-8}alkyl; C_{3-6}cycloalkyl; C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl,

C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, -NO_2, -NH_2, -SR^6, -$S(O)_2R^6$, -$S(O)R^7$, -$S(O)_2R^7$, -$C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, -CF_3, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; -NH_2; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, -OR^{11}, -$S(O)_2NR^8R^9$, and -$SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, -CF_3, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, -NO_2, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, -$C(O)NH_2$, -$S(O)R^7$, -$S(O)_2R^7$, -$C(O)R^7$, -$NS(O)_2R^7$, -$S(O)_2NR^8R^9$, -$S(O)_2NHR^{11}$, -$S(O)_2R^{11}$, -$S(O)_2NR^7COR^{11}$, -$S(O)_2NHCOR^{11}$, -$S(O)_2[COR^{11}]_n$ wherein n is 1, 2, or 3, -OR^{11} , -$OR^{11}OR^{11}$, -$C(O)R^{11}$, -$C(O)NR^{11}$, -$C(O)OR^{11}$, -NR^{11}, -$NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with -$C(O)R^{11}$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted

with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, alkoxy, $-S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, and C_{1-8}alkyl; heterocycle optionally substituted with heterocycleC_{1-8}alkyl; or C_{6-14}aryl optionally substituted with alkoxy;

R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;
or a pharmaceutically acceptable derivative thereof,
provided that

(a) when X is N; R^1 is C_{6-14}aryl substituted with halogen; R^2 and R^3 are hydrogen; R^5 is halogen; R^4 cannot be heterocycle substituted with C_{1-8}alkyl;

(b) when X is C; R^2 is hydrogen, halogen or C_{1-8}alkyl; R^3 is hydrogen; R^4 is C_{6-14}aryl substituted with halogen, hydroxy, or C_{1-8}alkyl; R^5 is hydrogen, halogen, C_{1-8}alkyl, or alkoxy; then R^1 cannot be C_{1-8}alkyl, C_{3-6}cylcoalkyl, or C_{6-14}aryl substituted with halogen, C_{1-8}alkyl, alkoxy, or C_{6-14}arylC_{2-6}alkenyl; and

(c) when X is C; R^2 is hydrogen or alkyl, R^3 is hydrogen, R^4 is C_{6-14}aryl substituted with halogen, CN, C_{1-8}alkyl, or $-NO_2$; R^5 is hydrogen, $-NO_2$ or NH_2, then R^1 cannot be C_{10-14} aryl substituted with alkoxy.

Preferred compounds of formula (I) are those wherein X is O.

More preferred compounds of formula (I) are those wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, -CN, $-SR^6$, $-S(O)_2R^6$; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, and C_{6-14}arylC_{1-8}alkyl; R^6 is C_{1-8}alkyl, optionally substituted with halogen; R^7 is C_{1-8} alkyl optionally substituted with one or more substituents selected from the group consisting of hydroxy; $-NH_2$, or heterocycle; R^2 is hydrogen; R^3 is hydrogen or C_{1-8} alkyl; R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of

oxo, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$, $S(O)_2NR^8R^9$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, and heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl and heterocycleC_{1-8}alkyl; $R^8$and R^9 are the same or different and are selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cycloalkyl; R^{10} is C_{1-8}alkyl; R^{11} is C_{1-8}alkyl, optionally substituted with $-SO_2NR^8R^9$; and R^5 is halogen or $-NO_2$; or a pharmaceutically acceptable derivative thereof.

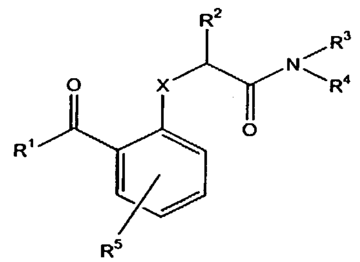
More preferred compounds of formula (I) are those wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, and -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, $-NO_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-NS(O)_2R^7$, wherein R^7 is $-NH_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

More preferred compounds of formula (I) are those wherein X is O; R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, CF_3, -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $S(O)_2NR^8R^9$, wherein $R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl.

Other preferred compounds of formula (I) are those wherein R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, and -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, $-NO_2$,

$-S(O)R^7$, $-S(O)_2R^7$, $-NS(O)_2R^7$, wherein R^7 is $-NH_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof provided that when X is C; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with halogen, CN, C_{1-8}alkyl, $-NO_2$; and R^5 is halogen, then R^1 cannot be C_{6-10}aryl substituted with alkoxy.

In another aspect of the present invention compounds of formula (IA) are disclosed:



(IA)

wherein:

X is C, O, or N;

R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-S(O)_2R^{11}$, $-S(O)_2NR^7COR^{11}$, $-S(O)_2NHCOR^{11}$, $-S(O)_2[COR^{11}]_n$ wherein n is 1, 2, or 3, $-OR^{11}$, $-OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, alkoxy, $-S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, and C_{1-8}alkyl; heterocycle optionally substituted with heterocycleC_{1-8}alkyl; or C_{6-14}aryl optionally substituted with alkoxy;

R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

or a pharmaceutically acceptable derivative thereof provided that

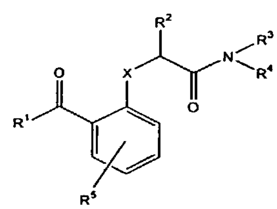
a) when X is C; R^2 is hydrogen, halogen or C_{1-8}alkyl; R^3 is hydrogen; R^4 is C_{6-14}aryl substituted with halogen, hydroxy, or C_{1-8}alkyl; R^5 is hydrogen, halogen, C_{1-8}alkyl, or alkoxy; then R^1 cannot be C_{1-8}alkyl, C_{3-6}cycloalkyl, or C_{6-14}aryl substituted with halogen, C_{1-8}alkyl, or C_{6-14}arylC_{2-6}alkenyl; and

(b) when X is C; R^2 is hydrogen or alkyl; R^3 is hydrogen; R^4 is C_{6-14}aryl substituted with halogen, CN, alkyl, or $-NO_2$; R^5 is hydrogen, $-NO_2$, or NH_2, then R^1 cannot be C_{10-14} aryl substituted with alkoxy.

Preferred compounds of formula (IA) are compounds wherein X is O.

More preferred compounds of formula (IA) are compounds wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, -CN, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, $-S(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, heterocycleC_{2-6}alkenyl, and heterocycle which may be optionally substituted with oxo; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

In a further aspect of the present invention there is provided compounds of formula (IB):



(IB)

wherein:

X is C, O, or N;

R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$, $-SR^{10}N(R^{10})_2$, and $-S(O)_2NR^8R^9$;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{10} is C_{1-8}alkyl;

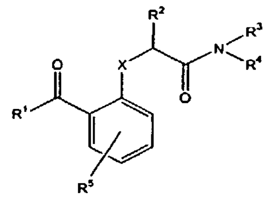
R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, alkoxy, $-S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, and C_{1-8}alkyl; heterocycle optionally substituted with heterocycleC_{1-8}alkyl; or C_{6-14}aryl optionally substituted with alkoxy;

R^5 is hydrogen, halogen,C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof provided that when X is N; R^1 is C_{6-14}aryl substituted with halogen; R^2 and R^3 are hydrogen; R^5 is halogen; R^4 cannot be heterocycle substituted with C_{1-8}alkyl.

Preferred compounds of formula (IB) are those wherein X is O.

More preferred compounds of formula (IB) are those wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, and -CN; R^2 is hydrogen; R^3 is hydrogen; R^4 is heterocycle; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

In another aspect of the present invention there is provided compounds of formula (IC)



(IC)

wherein:

X is C, O, or N;

R^1 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, halogen, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-S(O)_2R^{11}$, $-S(O)_2NR^7COR^{11}$, $-S(O)_2NHCOR^{11}$, $-S(O)_2[COR^{11}]_n$ wherein n is 1, 2, or 3, $-OR^{11}$, $-OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted

with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

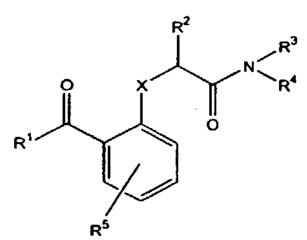
R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, alkoxy, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

Preferred compounds of formula (IC) are those wherein X is O.

More preferred compounds of formula (IC) are those wherein X is O; R^1 is heterocycle, optionally substituted with -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-OR^{11}$, and heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

The present invention also features compounds of formula (ID):



(ID)

wherein:

X is C, O, or N;

R^1 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, halogen, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$, $-S(O)_2NR^8R^9$, and $-SR^{10}N(R^{10})_2$; or R^3 and R^4 together with the nitrogen atom to which they are attached form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{10} is C_{1-8}alkyl;

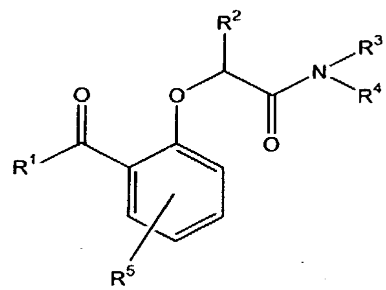
R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, and C_{1-8}alkyl;

R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

Preferred compounds of formula (ID) are those wherein X is O.

More preferred compounds of formula (ID) are those wherein X is O; R^1 is heterocycle; R^2 and R^3 are hydrogen; R^4 is heterocycle; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

In a further aspect of the present invention there is provided compounds of formula (II):



(II)

wherein:

R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

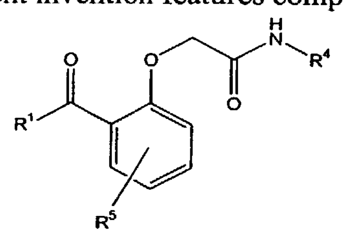
R^3 and R^4 form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$;

provided that when R^1 is unsubstituted C_{6-14}aryl, then R^3R^4 is substituted.

R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

Preferred compounds of formula (II) are those wherein R^1 is C_{6-14}aryl which is substituted with halogen; R^2 is hydrogen; R^3 and R^4 form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

A further aspect of the present invention features compounds of formula (III):



(III)

wherein:

R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-S(O)_2NHR^{11}$, $S(O)_2R^{11}$, $OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $-C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

$R^8$and R^9 are independently selected from the group consisting of hydrogen; C_{3-6}cycloalkyl; C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl; or $-C(O)NH_2$;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, alkoxy, $-S(O)_2NR^8R^9$, $-NR^8R^9$ and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen; halogen; C_{1-8}alkyl; $-NO_2$; $-NH_2$; C_{1-8}alkylamino; CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof,

provided that:

(a) when R^4 is C_{6-14}aryl substituted with OR^{11} wherein R^{11} is NR^8R^9 wherein R^8 and R^9 are C_{1-8}alkyl, and R^1 is C_{6-14}aryl, then R^1 cannot be substituted in the para position, and

(b) R^1 and R^4 cannot both be unsubstituted.

Preferred compounds of formula (III) are those wherein R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, -CN, $-SR^6$, $-S(O)_2R^6$; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, and C_{6-14}arylC_{1-8}alkyl; R^6 is C_{1-8}alkyl, optionally substituted with halogen; R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, $-NH_2$, or heterocycle; R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, $-C(O)NH_2$, $-S(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; $R^8$and R^9 are the same or different and are selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cycloalkyl; R^{10} is C_{1-8}alkyl; R^{11} is C_{1-8}alkyl, optionally substituted with $-S(O)_2NR^8R^9$; and R^5 is halogen or $-NO_2$; or a pharmaceutically acceptable derivative thereof.

More preferred compounds of formula (III) are those wherein R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, and -CN; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, $-NO_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-NS(O)_2R^7$, wherein R^7 is $-NH_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

The present invention further features compounds of formula (I), wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent

selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

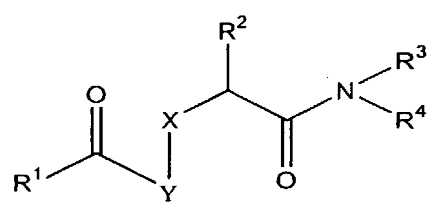
R^3 is hydrogen;

R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

The present invention also features compounds of formula (IV)



(IV)

wherein:

X is C, O, or N;

Y is heterocycle optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, $-CF_3$, or alkoxy;

R^1 is C_{1-8}alkyl; C_{3-6}cycloalkyl; C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen,or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, OR^{11} and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NSO_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cycloalkyl;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-SO_2NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen, halogen,C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

Preferred compounds of formula (IV) are compounds wherein Y is a heterocycle substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, $-CF_3$, or alkoxy; or a pharmaceutically acceptable derivative thereof. More preferred compounds of formula (IV) are compounds wherein X is O. Most preferred compounds of formula (IV) are those wherein X is O and Y is a heterocycle substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, $-CF_3$, or alkoxy; or a pharmaceutically acceptable derivative thereof.

Preferred compounds of the present invention include:

2-[2-(1-benzothiophen-2-ylcarbonyl)-4-chlorophenoxy]-N-phenylacetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1H-imidazol-1-yl)phenyl]acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1H-1,2,4-triazol-1-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(4-morpholinyl)phenyl]acetamide;

N-[4-(aminosulfonyl)phenyl]-2-(2-benzoyl-4-chlorophenoxy)acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[(1,3-thiazol-2-ylamino)sulfonyl]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(4-methyl-1-piperazinyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(hydroxymethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[(methylamino)sulfonyl]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1,1-dioxo-1lambda~6~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(4-morpholinyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[3-(dimethylamino)propoxy]-2-methylphenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-5-yl)acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(4-morpholinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[3-(1H-imidazol-1-yl)propoxy]-2-methylphenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-{2-methyl-4-[3-(4-morpholinyl)propoxy]phenyl}acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-oxo-1lambda~4~,4-thiazinan-4-yl)propoxy]phenyl}acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(2-benzoyl-4-chlorophenoxy)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]acetamide;

2-[2-(1-benzofuran-2-ylcarbonyl)-4-chlorophenoxy]-N-phenylacetamide

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-phenylacetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(2-furoyl)phenoxy]acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-(1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3-furoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-{4-chloro-2-[(1-methyl-1H-pyrrol-2-yl)carbonyl]phenoxy}-N-phenylacetamide;

2-(4-chloro-2-{[5-(2-pyridinyl)-2-thienyl]carbonyl}phenoxy)-N-phenylacetamide;

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-pyridinylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(2-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(4-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[2-(2-bromobenzoyl)-4-chlorophenoxy]acetamide;

2-{4-chloro-2-[(5-methyl-3-isoxazolyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]acetamide;

2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}acetamide;

2-{4-chloro-2-[3-(trifluoromethyl)benzoyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(3-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[2-(3-bromobenzoyl)-4-chlorophenoxy]acetamide;

2-[4-chloro-2-(3-methylbenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-pyridinylcarbonyl)phenoxy]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(1-methyl-1H-imidazol-2-yl)carbonyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide

N-(1,3-benzothiazol-6-yl)-2-(2-benzoyl-4-chlorophenoxy)acetamide

2-(4-chloro-2-{3-[(trifluoromethyl)sulfanyl]benzoyl}phenoxy)-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide

2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

N-(1,3-benzothiazol-6-yl)-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-(2-methyl-1,3-benzothiazol-5-yl)acetamide

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(4-chloro-2-{3-[(trifluoromethyl)sulfanyl]benzoyl}phenoxy)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(methylsulfonyl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-(2-cyclopentylethynyl)benzoyl]phenoxy}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-(2-phenylethynyl)benzoyl]phenoxy}acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

N-(1,2-benzisothiazol-5-yl)-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-1-(2,3-dihydro-1H-indol-1-yl)-1-ethanone;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

N-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide;

2-{2-[3,5-bis(trifluoromethyl)benzoyl]-4-chlorophenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{2-[(5-bromo-3-pyridinyl)carbonyl]-4-chlorophenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(6-methyl-1,3-benzothiazol-5-yl)acetamide;

N-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(4-chloro-2-{3-[(trifluoromethyl)sulfonyl]benzoyl}phenoxy)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[4-(1,3-thiazol-2-yl)phenyl]acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[4-(1,3-oxazol-2-yl)phenyl]acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-{4-[(3-hydroxypropyl)sulfonyl]-2-methylphenyl}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(2-methyl-4-{3-[(methylamino)sulfonyl]propoxy}phenyl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(4-{3-[(dimethylamino)sulfonyl]propoxy}-2-methylphenyl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{2-[(5-bromo-3-pyridinyl)carbonyl]-4-chlorophenoxy}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-{4-[3-(1H-imidazol-1-yl)propoxy]-2-methylphenyl}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-{2-methyl-4-[(E)-4-(1-pyrrolidinyl)-1-butenyl]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[6-(aminosulfonyl)-4-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dimethylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-ethylbenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]-*N*-{4-[3-(2,5-dihydro-1*H*-pyrrol-1-yl)propoxy]-2-methylphenyl}acetamide hydrochloride;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(6-cyano-2-pyridinyl)carbonyl]phenoxy}acetamide;

N-[6-(aminosulfonyl)-2-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dicyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-cyano-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

and pharmaceutically acceptable derivatives thereof.

Preferred compounds of the present invention include compound number 7, 32, 33, 36, 38, 44, 45, 49, 51, 52, 61, 65, 66, 71, 75, 76, 111, 112, 115, 118, 119, 128, 129, 171, 172, 191, 192, 199, 200, 206, 207, 224, 225, 232; 233, 235, 236, 246, 247, 253, 254, 255, 256, 259, 260, 261, 262, 264, 265, 267, 268, 288, 289, 290, 409, 412, 428, 430, 431, 433, 491, 564, 587, 475, 478, 498, 593, 483, 637, 503, 601, 658 and pharmaceutically acceptable derivatives thereof.

More preferred compounds of the present invention are selected from the group consisting of N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide, N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-fluoro-5-(trifluoromethyl)benzoyl]acetamide; N-{4-[3-(aminosulfonyl)propoxy] -2-methylphenyl}-2-{4-chloro-2-[3-fluoro-5-(trifluomethyl)benzoyl]phenoxy}acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-fluorobenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide, *N*-[6-(aminosulfonyl)-4-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-cyanobenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dimethylbenzoyl)phenoxy]acetamide,
N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-ethylbenzoyl)phenoxy]acetamide, 2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]-*N*-{4-[3-(2,5-dihydro-1*H*-pyrrol-1-yl)propoxy]-2-methylphenyl}acetamide hydrochloride, *N*-

[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-methylbenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(6-cyano-2-pyridinyl)carbonyl]phenoxy}acetamide, *N*-[6-(aminosulfonyl)-2-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide, *N*-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dicyanobenzoyl)phenoxy]acetamide and pharmaceutically acceptable derivatives thereof.

Compounds of the present invention that are advantageous are those wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl, in addition to one or more other substituents as defined above.

The term "alkyl", alone or in combination with any other term, refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

The term "alkenyl," alone or in combination with any other term, refers to a straight-chain or branched-chain alkyl group with at least one carbon-carbon double bond. Examples of alkenyl radicals include, but are not limited to, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, hexadienyl and the like.

The term "alkynyl" refers to hydrocarbon groups of either a straight or branched configuration with one or more carbon-carbon triple bonds which may occur in any stable point along the chain, such as ethynyl, propynyl, butynyl, pentynyl, and the like.

The term "alkoxy" refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

The term "aryl," alone or in combination with any other term, refers to a carbocyclic aromatic radical (such as phenyl or naphthyl) containing the specified number of carbon atoms, preferably from 6-14 carbon atoms, and more preferably from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, indanyl, azulenyl, fluorenyl, anthracenyl and the like.

The term "heterocycle" or "heterocyclic" as used herein, refers to a 3-to 7- membered monocyclic heterocyclic ring or 8-to 11- membered bicyclic heterocyclic ring which is either saturated, partially saturated or unsaturated, and which may be optionally benzofused if monocyclic. Each heterocycle consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any carbon or heteroatom which results in the creation of a stable structure. Preferred heterocycles include 5-7 membered monocyclic heterocycles and 8-10 membered bicyclic heterocycles. Examples of such groups include imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoqinolyl, indolyl, indazolyl, indazolinolyl, perhydropyridazyl, pyridazyl, pyridyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, pyranyl, pyrazolinyl, piperazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, oxazolyl, benzoxazolyl, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl, azepinyl, isoxozolyl, isothiazolyl, furazanyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thiadiazoyl, dioxolyl, dioxinyl, oxathiolyl, benzodioxolyl, dithiolyl, thiophenyl, tetrahydrothiophenyl, sulfolanyl, dioxanyl, dioxolanyl, tetahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, tetradyrofurofuranyl and tetrahydropyranofuranyl.

Preferred heterocycles include imidazolidinyl, indazolyl, pyrrolidinyl, thiamorpholinyl, thiophenyl, furyl, benzofuranyl, thiazolyl, oxazolyl, pyrrolyl, indolinolyl, benzthiazolyl, pyridinolyl, quinolinoyl, and benzothiophenyl.

The term "halogen" refers to a radical of fluorine, chlorine, bromine or iodine.

The term "pharmaceutically effective amount" refers to an amount effective in treating a virus infection, for example an HIV infection, in a patient either as monotherapy or in combination with other agents. The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient, or the improvement of an ascertainable measurement associated with a particular disorder, and may include the suppression of symptom recurrance in an asymptomatic patient such as a patient in whom a viral infection has become latent. The term "prophylactically effective amount" refers to an amount effective in preventing a virus infection, for example an HIV infection, or preventing the occurrence of symptoms of such an infection, in a patient. As used herein, the term "patient" refers to a mammal, including a human.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the antiviral agent.

As used herein, the compounds according to the invention are defined to include pharmaceutically acceptable derivatives thereof. A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

Pharmaceutically acceptable salts of the compounds according to the invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicyclic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g., magnesium), ammonium and NW+4 (wherein W is C_{1-4} alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts or organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4}alkyl group).

Esters of the compounds according to the invention are independently selected from the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms, Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group.

Any reference to any of the above compounds also includes a reference to a pharmaceutically acceptable salts thereof.

In a further aspect of the invention there are provided the compounds according to the invention for use in medical therapy particularly for the treatment or prophylaxis of viral infections such as an HIV infection. Compounds according to the invention have been shown to be active against HIV infections, although these compounds may be active against HBV infections as.well.

The compounds according to the invention are particularly suited to the treatment or prophylaxis of HIV infections and associated conditions. Reference herein to treatment extends to prophylaxis as well as the treatment of established infections, symptoms, and associated clinical conditions such as AIDS related complex (ARC), Kaposi's sarcoma, and AIDS dementia.

According to a particular embodiment of the present invention, there is provided a method of treatment of HIV mutant viruses that exhibit NNRTI drug resistance by administering a thereapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable derivative thereof to a mammal, in particular a human. In particular, the compounds of the present invention may be used to treat wild-type HIV-1 as well as several resistance mutations, for example, K103N, L1001, or Y181C.

According to another aspect, the present invention provides a method for the treatment or prevention of the symptoms or effects of a viral infection in an infected animal, for example, a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a compound according to the invention. According to

a particular embodiment of this aspect of the invention, the viral infection is a retorviral infection, in particular an HIV infection. A further aspect of the invention includes a method for the treatment or prevention of the symptoms or effects of an HBV infection.

The compounds according to the invention may also be used in adjuvant therapy in the treatment of HIV infections or HIV-associated symptoms or effects, for example Kaposi's sarcoma.

The present invention further provides a method for the treatment of a clinical condition in an animal, for example, a mammal including a human which clinical condition includes those which have been discussed in the introduction hereinbefore, which comprises treating said animal with a therapeutically effective amount of a compound according to the invention. The present invention also includes a method for the treatment or prophylaxis of any of the aforementioned infections or conditions.

In yet a further aspect, the present invention provides the use of a compound according to the invention in the manufacture of a medicament for the treatment or prophylaxis of any of the above mentioned viral infections or conditions.

The above compounds according to the invention and their pharmaceutically acceptable derivatives may be employed in combination with other therapeutic agents for the treatment of the above infections or conditions. Combination therapies according to the present invention comprise the administration of at least one compound of the present invention or a pharmaceutically acceptable derivative thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously in either the same or different pharmaceutical formulations or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Preferably the combination therapy involves the administration of one compound according to the invention and one of the agents mentioned herein below.

Examples of such further therapeutic agents include agents that are effective for the treatment of viral infections or associated conditions such as (1 alpha, 2 beta, 3 alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514], oxetanocin-G (3,4-bis-(hydroxymethyl)-2-oxetanosyl]guanine), acyclic nucleosides (e.g. acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir), acyclic nucleoside phosphonates (e.g. (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC), PMEA, ribonucleotide reductase inhibitors such as 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl) thiocarbonohydrazone, 3'azido-3'-deoxythymidine, other 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-didehydrothymidine, protease inhibitors such as indinavir, ritonavir, nelfinavir, amprenavir, oxathiolane nucleoside analogues such as (-)-<u>cis</u>-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine) or <u>cis</u>-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclopropylamino)-9<u>H</u>-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), ribavirin, 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), tat inhibitors such as 7-chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2-(<u>H</u>)one (Ro5-3335), 7-chloro-1,3-dihydro-5-(1H-pyrrol-2yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429), interferons such as α-interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyridamole; pentoxifylline, N-acetylcysteine (NAC), Procysteine, α -trichosanthin, phosphonoformic acid, as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD_4 and genetically engineered derivatives thereof, or other non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine (BI-RG-587), loviride (α -APA) and delavuridine (BHAP), and phosphonoformic acid, and 1,4-dihydro-2H-3,1-benzoxazin-2-ones NNRTIs such as (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726 or DMP-266), and quinoxaline NNRTIs such as isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate (HBY1293).

The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

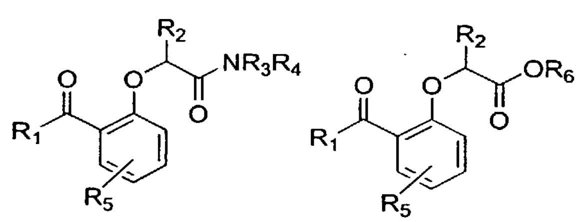
More preferably the combination therapy involves the administration of one of the above mentioned agents and a compound within one of the preferred or particularly preferred sub-groups within formulae (I) – (IV) (including IA, IB, IC and ID) as described above. Most preferably the combination therapy involves the joint use of one of the above named agents together with one of the compounds of the present invention specifically named herein.

The present invention further includes the use of a compound according to the invention in the manufacture of a medicament for simultaneous or sequential administration with at least one other therapeutic agent, such as those defined hereinbefore.

The compounds of the present invention may be synthesized by the following methods or by any method known in the art.

The compounds of the present invention may be prepared according to representative Schemes I-XXXIV, which are presented below. The compounds, which may be prepared according to these schemes, are not limited by the compounds contained in the schemes or by any particular substituents used in the schemes for illustrative purposes.

Compounds of formula (I) wherein R_1 is hereinbefore defined, can be readily prepared from compounds of formula IV and V wherein R_1, R_2, R_3, R_4, and R_5 are as hereinbefore defined and R_6 is hydrogen, using suitable coupling conditions known in the art.

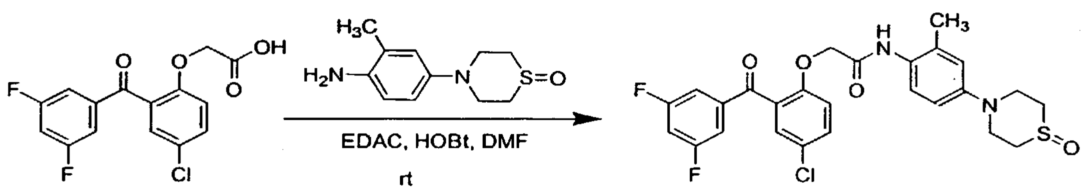


NHR_3R_4

I IV V

For example, compounds of formula IV can be allowed to react with compounds of formula V in the presence of a suitable dehydrating agent, such as a carbodiimide, dicyclohexylcarbodiimide (DCC) for example, or more preferably 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC). In addition, the presence of a suitable activating agent, such as 1-hydroxybenztriazole (HOBt), is usually required to promote efficient coupling of the carboxylic acid to the appropriate amine. These reactions are typically carried out in an aprotic solvent such as acetonitrile, tetrahydrofuran or more preferably N,N-dimethylformamide (DMF), at temperatures from 0 °C to 150 °C, most preferably at ambient temperatures. For example, carboxylic acid **49** (Scheme I) is allowed to react with amine **399** in DMF and in the presence of EDAC and HOBt at ambient temperature to provide compound **46**.

Scheme I

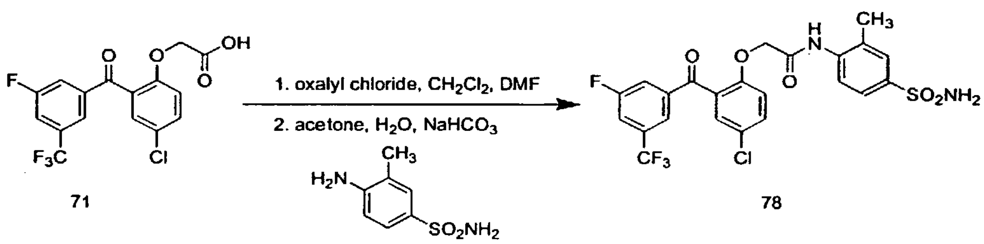


49 46

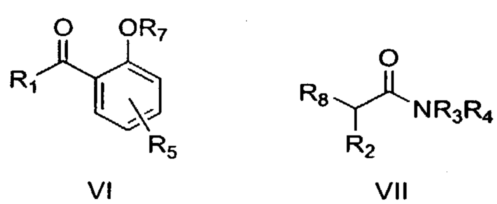
Alternatively, compounds of formula IV, wherein R_1, R_2, and R_5 are as hereinbefore defined, can first be converted to the corresponding acid chloride which is then allowed to react with compounds of formula V, wherein R_3 and R_4 are as hereinbefore defined, to afford compounds of (I). The preparation of the desired acid chloride can be accomplished by methods well-known in the art. The carboxylic acids can be allowed to react with a suitable dehydrating agent such as thionyl chloride or more preferably oxalyl chloride. These reactions are typically performed in an aprotic solvent such as acetonitrile or pyridine or a chlorinated solvent such as chloroform or more preferably dichloromethane. The corresponding acid chlorides are not typically isolated in pure form, but instead are allowed to react directly with compounds of formula V. Most often, reactions of the acid chlorides are performed in an aprotic solvent such as acetonitrile or chloroform, or more preferably in acetone. In addition, the presence of a compound capable of acting as a base such as triethylamine or pyridine, or more preferably sodium bicarbonate, is required in order to obtain sufficient yields of the coupling products. When

inorganic bases such as sodium bicarbonate are used, the addition of a small amount of water to the reaction mixture promotes an efficient coupling reaction. For example, carboxylic acid **71** (Scheme II) is allowed to react with oxalyl chloride in dichloromethane and in the presence of a catalytic amount of DMF to afford the corresponding acid chloride. The acid chloride is then allowed to react with amine **466** in a mixture of acetone and water and in the presence of an excess of sodium bicarbonate to provide compound **78**

Scheme II

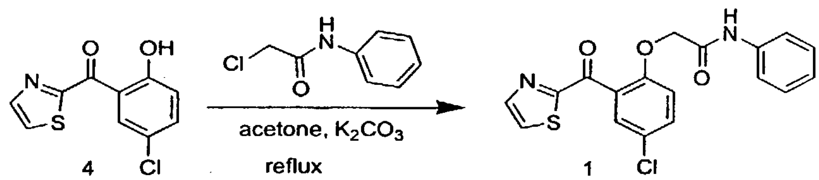


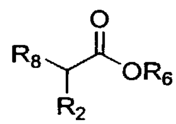
Lastly, compounds of formula I in which $R_1 - R_5$ are as hereinbefore defined, can be readily prepared by reaction of compounds of formula VI, wherein R_7 is hydrogen with compounds of formula VII wherein R_2, R_3 and R_4 are as hereinbefore defined, and R_8 is a suitable leaving group such as a halogen, preferably chlorine or bromine, or a methanesulfonate or para-toluenesulfonate ester.



The alkylation of compounds of formula VI by compounds of formula VII are typically performed in an aprotic solvent such as acetonitrile, DMF or more preferably in acetone. In addition, the presence of a compound capable of acting as a base such as triethylamine, pyridine, or more preferably sodium carbonate, is usually required to promote efficient reaction. Furthermore, the reactions are typically carried out at elevated temperatures in the range of 40-100 °C. For example, phenol **4** (Scheme III) is allowed to react with 2'-chloroacetanilide in the presence of sodium carbonate in refluxing acetone to provide compound **1**.

Scheme III



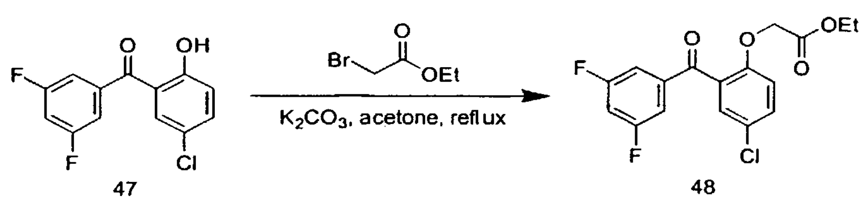


VIII

Compounds of formula IV, wherein R_1, R_2 and R_5 are as hereinbefore defined and R_6 is C_{1-6}alkyl, can be prepared by reaction of compounds of formula VI, wherein R_1 and R_5 are as hereinbefore defined, and R_7 is hydrogen, with those of formula VIII, wherein R_6 is C_{1-6}alkyl, R_2 is as hereinbefore defined, and R_8 is a suitable leaving group such as a halogen, preferably chlorine or bromine, or a methanesulfonate or para-toluenesulfonate ester. Typically, the reactions are performed in an aprotic solvent such as acetonitrile, DMF, or more preferably acetone, and temperatures ranging from 40 °C to 100 °C. In addition, the presence of an excess of a base such as triethylamine, pyridine, or more preferably potassium carbonate, is usually required for efficient reaction. For example, phenol **47** (Scheme IV) is allowed to react with ethyl bromoacetate in refluxing acetone and in the presence of potassium carbonate to afford ester **48.**

Compounds of formula VIII are either commercially available or can be prepared using literature methods that are known in the art.

Scheme IV

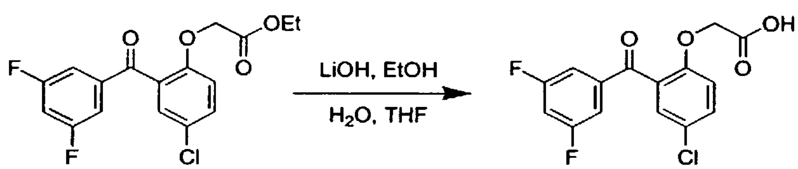


Compounds of formula IV, in which R_1, R_2 and R_5 are as hereinbefore defined and R_6 is hydrogen can be prepared from compounds of formula IV in which R_1, R_2 and R_5 are as hereinbefore defined and R_6 is C_{1-6}alkyl, by reaction with aqueous base or other suitable

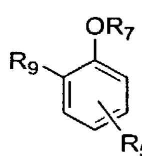
methods known in the art. A variety of inorganic bases can be used to affect the saponification of the esters of formula IV, such as sodium carbonate, sodium hydroxide or more preferably lithium hydroxide. Typically, these reactions are performed in water in addition to a solvent that is miscible with water and is capable of dissolving the compounds of formula IV such as tetrahydrofuran, methyl alcohol or ethyl alcohol.

For example, ester **48** (Scheme V) is allowed to react with lithium hydroxide in a mixture of THF, water, and ethanol to afford carboxylic acid **49**.

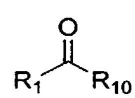
Scheme V



Below are schemes showing the preparation of compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined, and R_7 is either hydrogen or methyl. Compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl, can be prepared by reaction of compounds of formula IX, wherein R_5 is as hereinbefore defined, and R_7 is methyl with those of formula X, wherein R_1 and R_{10} are as hereinbefore defined, with the further stipulation that these groups are chemically compatible with the reaction conditions, R_7 is methyl, R_9 is a halogen, preferably bromine or iodine, and R_{10} is N,O-dimethylhydroxylamino.



IX

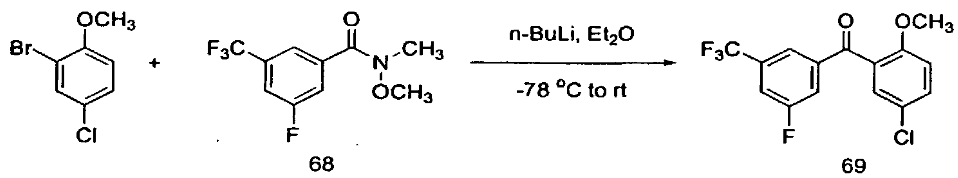


X

Typically, compounds of formula IX are treated with an agent capable of effecting a halogen-metal exchange reaction, such as sec-butyl lithium, methyl lithium, tert-butyl lithium, or more preferably n-butyl lithium. The halogen-metal exchange can be performed in an ethereal solvent such as THF, dioxane or more preferably diethyl ether, and at low temperatures ranging from -100 °C to 0 °C, most preferably -78 °C. When the halogen-metal exchange reaction is complete, the resulting compounds of formula IX, in which R_9 is lithium, are allowed to react with compounds of formula X, again in an ethereal solvent and at low temperatures. For example, 2-bromo-4-chloroanisole (Scheme

VI) in diethyl ether is treated with n-butyl lithium at -78 °C. After 15 minutes at -78 °C, the resulting lithium species is allowed to react with amide **68** to afford the desired ketone **69**.

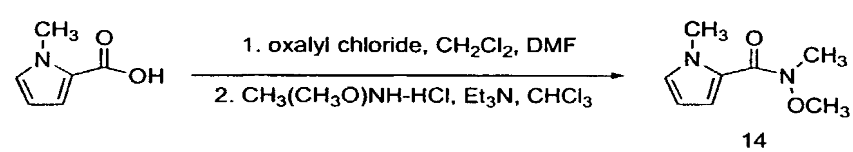
Scheme VI



Compounds of formula IX, in which R_5 is as hereinbefore defined, R_7 is methyl and R_9 is either bromine or iodine are either commercially available or can be prepared using literature methods known in the art.

Compounds of formula X, in which R_1 is as hereinbefore defined and R_{10} is N,O-dimethylhydroxylamino, can be prepared from compounds of formula X in which R_{10} is a suitable leaving group, preferably chlorine, by reaction with N,O-dimethylhydroxylamine in an aprotic solvent, preferably acetonitrile, chloroform or dichloromethane, and in the presence of a base, preferably triethylamine. Compounds of formula X in which R_{10} is chlorine can be prepared from compounds of formula X, in which R_{10} is hydroxy, using literature methods known in the art, such as reaction with oxalyl chloride in an aprotic solvent, preferably dichloromethane or chloroform and in the presence of a catalytic amount of DMF. For example, 1-methyl-2-pyrrolecarboxylic acid (Scheme VII) in dichloromethane is allowed to react with excess oxalyl chloride in the presence of a catalytic amount of DMF. The resulting acid chloride is not isolated in pure form, but instead is allowed to react with N,O-dimethylhydroxylamine in chloroform and in the presence of triethylamine, to afford amide **14**.

Scheme VII

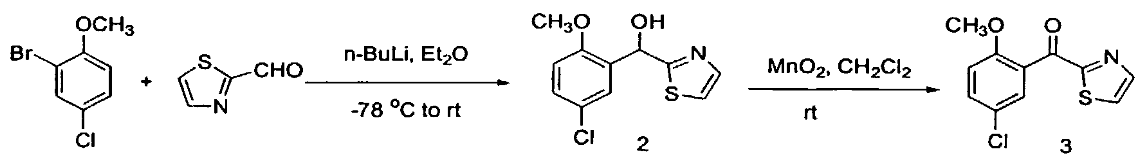


Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl can be prepared by reaction of compounds of formula IX with those of formula X, wherein R_1 and R_5 are as hereinbefore defined with the further stipulation that these groups are chemically compatible with the reaction conditions, R_7 is methyl, R_9 is a halogen, preferably bromine or iodine, and R_{10} is N,O-dimethylhydroxylamino. Compounds of formula IX can be converted to a species in which R_9 is a magnesium halide, such as magnesium bromide or magnesium iodide, so-called Grignard reagents. The species containing the magnesium halide is then allowed to react with compounds of formula X, in which R_{10} is N,O-dimethylhydroxylamino. These reactions are typically performed in ethereal solvents such as THF, dioxane or diethyl ether and at temperatures from 0 °C to 100 °C, preferably ambient temperature. The preparation of compounds of formula IX in which R_9 is a magnesium halide can be accomplished by literature methods known in the art. Typically, a compound of formula IX, in which R_9 is either bromine or iodine, is allowed to react with elemental magnesium in an aprotic, ethereal solvent.

Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl, can be prepared from compounds of formula IX, in which R_5 is as hereinbefore defined, R_7 is methyl and R_9 is a halogen, preferably bromine or iodine, by reaction with compounds of formula X, in which R_1 is as hereinbefore defined and R_{10} is hydrogen, with the further stipulation that R_1 is chemically compatible with subsequent reaction conditions. Compounds of formula X, in which R_1 is as hereinbefore defined and R_{10} is hydrogen, are either commercially available or can be prepared using literature methods known in the art. Compounds of formula IX, in which R_9 is either bromine or iodine, are first treated with an agent capable of effecting a halogen-metal exchange reaction, preferably n-butyl lithium, in an ethereal solvent, preferably diethyl ether, and at low temperatures, preferably - 78 °C. After the compound of formula IX, in which R_9 is lithium, has formed, it is allowed to react with compounds of formula X, in which R_{10} is hydrogen, to afford an intermediate alcohol species. Subsequently, the intermediate alcohol can be treated with an agent capable of oxidizing the alcohol to a compound of formula VI, the preferred oxidizing agent being manganese (IV) oxide. Typically, the oxidation reactions are performed in an aprotic solvent, preferably chloroform or dichloromethane, and at ambient temperatures. For example, 2-bromo-4-chloroanisole was

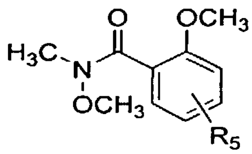
treated with n-butyl lithium in ether and at -78 °C. The resulting lithio species is then allowed to react with 2-thiazolecarboxaldehyde to afford intermediate alcohol **2**. Alcohol **2** is then allowed to react with an excess of manganese dioxide in dichloromethane at room temperature to afford ketone **3**

Scheme VIII

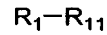


Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl, can be prepared by reaction of compounds of formula IX with those of formula X, wherein R_1 and R_5 are as hereinbefore defined, with the further stipulation that these groups are chemically compatible with the reaction conditions, R_7 is methyl, R_9 is a halogen, preferably bromine or iodine, and R_{10} is hydrogen. Compounds of formula IX can be converted to a species in which R_9 is a magnesium halide, such as magnesium bromide or magnesium iodide, so-called Grignard reagents. The species containing the magnesium halide is then allowed to react with compounds of formula X, in which R_{10} is hydrogen, to afford an intermediate alcohol. These reactions are typically performed in ethereal solvents such as THF, dioxane or diethyl ether and at temperatures from 0 °C to 100 °C, preferably ambient temperature. The preparation of compounds of formula IX, in which R_9 is a magnesium halide, can be accomplished by literature methods known in the art. Typically, a compound of formula IX, in which R_9 is either bromine or iodine, is allowed to react with elemental magnesium, in an aprotic, ethereal solvent. The intermediate alcohol is then allowed to react with an agent capable of oxidizing it to the desired ketone, preferably manganese (IV) oxide, in an aprotic solvent, preferably dichloromethane or chloroform, and at ambient temperature.

Lastly, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl, can be prepared by reaction of compounds of formula XII, in which R_5 is as hereinbefore defined, with compounds of formula XIII, in which R_1 is as hereinbefore defined, and R_{11} is a halogen, preferably bromine or iodine, with the further stipulation that R_1 and R_5 are chemically compatible with subsequent chemical steps.



XII



XIII

Typically, compounds of formula XIII, in which R_{11} is a halogen, preferably iodine or bromine, are treated with an agent capable of effecting a halogen-metal exchange reaction, preferably n-butyl lithium, in an ethereal solvent, preferably diethyl ether and at low temperature, preferably -78 °C.

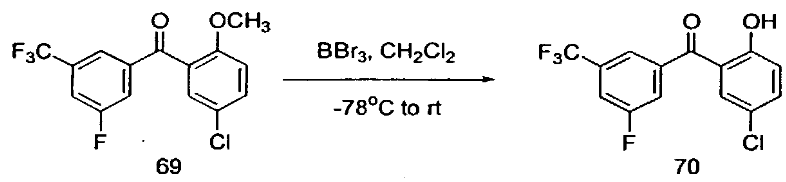
Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is methyl, can be prepared by reaction of compounds of formula XII with those of formula XIII, wherein R_1 and R_5 are as hereinbefore defined, with the further stipulation that these groups are chemically compatible with the reaction conditions, and R_{11} is a halogen, preferably bromine or iodine. Compounds of formula XIII can be converted to a species in which R_{11} is a magnesium halide, such as magnesium bromide or magnesium iodide, so-called Grignard reagents. The species containing the magnesium halide is then allowed to react with compounds of formula XII to afford the desired ketone. These reactions are typically performed in ethereal solvents such as THF, dioxane or diethyl ether and at temperatures from 0 °C to 100 °C, preferably ambient temperature. The preparation of compounds of formula XIII, in which R_{11} is a magnesium halide, can be accomplished by literature methods known in the art. Typically, a compound of formula XIII in which R_{11} is either bromine or iodine is allowed to react with elemental magnesium, in an aprotic, ethereal solvent.

Compounds of formula XIII, in which R_{11} is a halogen, preferably bromine or iodine, are either commercially available or can be prepared by literature methods.

Compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined and R_7 is hydrogen, can be prepared from compounds of formula VI, in which R_7 is methyl, by reaction with agents capable of demethylating aryl methyl ethers, with the stipulation that R_1 and R_5 are chemically stable under these reaction conditions. Among the agents which may be used for demethylating aryl methyl ethers are trimethylsilyl iodide, Lewis acids such as aluminum chloride, or more preferably boron tribromide. These reactions are typically conducted in aprotic solvents such as chloroform or dichloromethane and at temperatures from -78 ° to 100 °C, preferably from -78 °C to ambient temperature. For

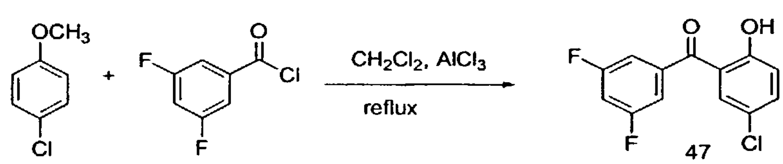
example, ketone **69** (Scheme IX) is allowed to react with an excess of boron tribromide in dichloromethane at -78 °C to afford phenol **70**.

Scheme IX



Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore defined, and R_7 is hydrogen, can be prepared by reaction of compounds of formula IX, in which R_5 is as hereinbefore defined, R_9 is hydrogen and R_7 is methyl, with compounds of formula X, in which R_1 is as hereinbefore defined, and R_{10} is a halogen, preferably chlorine, with the further stipulation that R_1 and R_5 are chemically compatible with the reaction conditions. These reactions, typically called Friedel-Craft acylations, are performed in an aprotic solvent such as nitrobenzene, 1,2-dichloroethane, sulfolane, or more preferably dichloromethane, at temperatures ranging from 0 °C to 150 °C, preferably 35-60 °C. In addition, the use of a compound which is capable of acting as a Lewis acid, such as titanium (IV) chloride, tin (IV) chloride, or more preferably aluminum chloride is required. For example, 4-chloroanisole (Scheme X) is allowed to react with 3,5-difluorobenzoyl chloride in refluxing dichloromethane in the presence of aluminum chloride to afford ketone **47**.

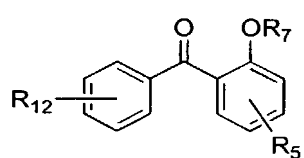
Scheme X



Compounds of formula X, in which R_1 is as hereinbefore defined, and R_{10} is a halogen, are either commercially available or can be prepared by literature methods. Alternatively, compounds of formula VI, in which R_1 and R_5 are as hereinbefore described and R_7 is hydrogen, can prepared from the reaction of compounds of formula IX, in which R_5 is as hereinbefore defined, and R_7 and R_9 are hydrogen, with compounds of formula X, in which R_1 in as hereinbefore defined and R_{10} is a halogen, preferably chlorine. These

reactions, typically called Fries rearrangements, are performed in an aprotic solvent, such as nitrobenzene, sulfolane or chloroform and at temperatures ranging from 0 °C to 150 °C. In addition, the reaction typically requires the presence of a compound capable of acting as a Lewis acid, such as aluminum chloride. Compounds of formula IX, in which R_5 is as hereinbefore defined, and R_9 and R_7 are hydrogen, are either commercially available or can be prepared by literature methods which are familiar to those skilled in the art.

Compounds of formula VI in which R_1 is C_{6-14} aryl or C_{6-14}heterocycle, substituted with C_{2-8} alkenyl, can be prepared from compounds of formula XIV, wherein R_5 is as hereinbefore defined, R_7 is hydrogen, methyl or methylene carboxyl ester and R_{12} is a group capable of undergoing a palladium-catalyzed reaction, such as bromine, iodine, or trifluoromethanesulfonate ester, by reaction with C_{2-8} alkenes. These reactions are typically conducted in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium, palladium dichloride bis(acetonitrile), or more preferably palladium acetate. The solvents for these reactions are typically aprotic solvents such as acetonitrile, or more preferably DMF. The reactions are usually performed at temperatures ranging from ambient temperature to 130 °C, preferably 50-90 °C. In addition, the presence of a base such as potassium or sodium carbonate, or triethylamine, is usually required. Lastly, reactions of some substrates may require the addition of a compound which is capable of stabilizing any intermediate palladium species. These compounds are most often triaryl arsine or phosphine derivatives, such as triphenylphosphine, or tri-ortho-tolylphosphine.



XIV

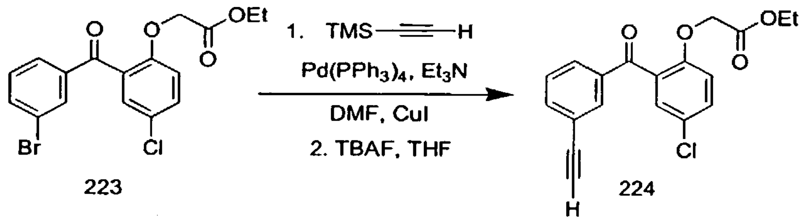
The C_{2-8} alkenes used in these reactions are either commercially available or can be prepared using literature methods which are familiar to those skilled in the art.

Compounds of formula XIV in which R_7, and R_5 are as hereinbefore defined and R_{12} is a group capable of undergoing a palladium-catalyzed reaction, such as bromine, iodine, or trifluoromethanesulfonate ester, are either commercially available or can be prepared by literature methods .

Compounds of formula VI in which R_1 is C_{6-14} aryl or C_{6-14}heterocycle, substituted with C_{2-8} alkyl, can be prepared from compounds of formula VI in which R_1 is C_{6-14} aryl, substituted with C_{2-8} alkenyl, by reaction with agents capable of selectively reducing the alkene bond. Among the agents that may be used to effect the desired reduction are palladium on carbon and Raney nickel. In addition, the presence of a reducing agent such as ammonium formate or pressurized hydrogen gas is required. These reactions are typically performed in a solvent capable of dissolving the olefinic substrate such as ethyl acetate, acetone, methyl alcohol or ethyl alcohol.

Compounds of formula VI in which R_1 is C_{6-14} aryl or C_{6-14}heterocycle, substituted with C_{2-8} alkynyl groups, can be prepared from compounds of formula XIV, in which R_5 is as hereinbefore described, R_7 is hydrogen, methyl or methylene carboxyl ester and R_{12} is a group capable of undergoing a palladium-catalyzed reaction, preferably iodine or bromine, by reaction with C_{2-8} alkynes. These reactions are typically performed in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium, palladium dichloride bis(acetonitrile), or palladium acetate. The solvents for these reactions are typically aprotic solvents such as acetonitrile, or more preferably DMF. The reactions are usually performed at temperatures ranging from ambient temperature to 130 °C, preferably 50-90 °C. In addition, the presence of a base such as potassium or sodium carbonate, or triethylamine, is usually required. Furthermore, reactions of some substrates may require the addition of a compound which is capable of stabilizing any intermediate palladium species. These compounds are most often triaryl arsine or phosphine derivatives, such as triphenylphosphine, or tri-ortho-tolylphosphine. Lastly, these reactions require the presence of a catalytic amount of copper (I) iodide. For example, ester **223** (Scheme XI) is allowed to react with trimethylsilylacetylene, in the presence of tertakis(triphenylphosphine)palladium, triethylamine and copper (I) iodide, to afford the intermediate trimethylsilyl-protected product. Treatment of the intermediate with tetrabutylammonium fluoride in THF provides compound **224**

Scheme XI



The C_{2-8} alkynes used in these reactions are either commercially available or can be prepared by literature methods familiar to those skilled in the art.

Compounds of formula VI in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle substituted with an amino group, R_5 is as hereinbefore described, and R_7 is hydrogen, methyl or methylene carboxy ester can be prepared from compounds of formula VI, in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle substituted with nitro, by reaction with a combination of agents which are capable of reducing a nitro functionality to an amino group. Among these combination of agents are a metal containing compound, such as elemental iron, palladium or Raney nickel and a reducing agent, such as ammonium formate, formic acid, hydrochloric acid or pressurized hydrogen gas. These reactions are typically performed in a solvent such as ethyl acetate, acetone, methyl alcohol or ethyl alcohol and at temperatures ranging from 20 °C to 100 °C, preferably ambient temperature.

Compounds of formula VI, in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle, substituted with a nitro functionality, R_5 is as hereinbefore described and R_7 is hydrogen or methyl, can be prepared by methods previously described herein or by literature methods known in the art.

Compounds of formula VI, in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle substituted with $-SO_2R_{13}$, where R_5 is as previously defined, R_7 is hydrogen, methyl or methylene carboxy ester and R_{13} is C_{1-8} alkyl, which is optionally substituted with hydroxy, alkylamino, or halogen, can be prepared from compounds of formula VI in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle substituted with SR_{13}, by reaction with agents which are capable of oxidizing a sulfide to a sulfone. Among the agents which are capable of effecting the desired, selective oxidation are meta-chloroperbenzoic acid (m-CPBA), hydrogen peroxide in acetic acid and oxone. These reactions are typically conducted in solvents such as dichloromethane, chloroform, ethyl alcohol, water or a mixture of these solvents and in the temperature range from 0 °C to 100 °C.

Compounds of formula VI , in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle substituted with -SR_{13}, wherein R_{13} is as previously described herein, can be prepared from commercially available material or by literature methods familiar to those skilled in the art.

Compounds of formula VI, in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle substituted with nitrile, can be prepared from compounds of formula VI, in which R_1 is C_{6-14} aryl or C_{6-14} arylheterocycle substituted with a halogen, preferably bromine or iodine, by reaction with an agent or a combination of agents capable of replacing the halogen with a nitrile functional group. Among these agents are copper (I) cyanide or a palladium catalyst in combination with an appropriate cyanide source such as potassium cyanide, sodium cyanide, or zinc cyanide. Among the palladium agents that can be employed for this transformation are tertrakis(triphenylphosphine)palladium, palladium acetate, or palladium dichloride bis(acetonitrile). These reactions are typically conducted in aprotic solvents such as acetonitrile, or more preferably DMF, and in the presence of phosphine ligand, such as triphenylphosphine, and at temperatures from 20 °C to 150 °C, preferably 80-85 °C.

Compounds of formula VI, in which R_1 is as hereinbefore described, R_7 is hydrogen, methyl or methylene carboxy ester and R_5 is hydrogen, halogen, nitro, trifluoromethyl, C_{1-8} alkyl or alkoxy can be prepared from commercially available material using processes described herein or by literature methods familiar to those skilled in the art.

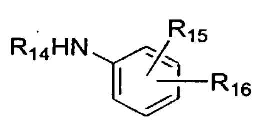
Compounds of formula VI, in which R_1 is as previously described, R_7 is hydrogen, methyl or methylene carboxy ester, and R_5 is amino, can be prepared from compounds of formula VI in which R_5 is nitro by reaction with agents or a combination of agents capable of reducing a nitro group to an amino functionality. Among these combination of agents are a metal containing compound, such as elemental iron, palladium or Raney nickel and a reducing agent, such as ammonium formate, formic acid, hydrochloric acid or pressurized hydrogen gas. These reactions are typically performed in a solvent such as ethyl acetate, acetone, methyl alcohol or ethyl alcohol and at temperatures ranging from 20 °C to 100 °C, preferably ambient temperature.

Compounds of formula VI in which R_1 is as hereinbefore defined, R_7 is hydrogen, methyl or methylene carboxy ester, and R_5 is C_{1-8} alkylamino can be prepared from compounds of formula VI in which R_5 is amino, by reaction with agents capable of

selectively alkylating the amino group. Among these agents are alkyl halides, such as methyl iodide, alkylsulfonate esters or alkylaryl sulfonate esters. These reactions are typically performed in polar, aprotic solvents such as N-methylpyrrolidine or DMF and at temperatures ranging from ambient to 150 °C.

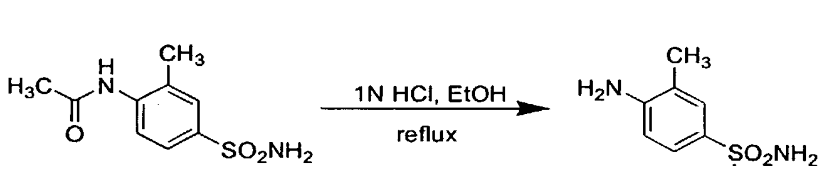
Compounds of formula V, in which R_3 and R_4, which may be the same or different, are hydrogen, hydroxy, C_{1-8}alkyl, heterocycle, C_{6-14}arylheterocycle or C_{6-14}aryl are commercially available or can be prepared by literature methods familiar to those skilled in the art.

Compounds of formula V, in which R_3 is hydrogen and R_4 is C_{6-14}aryl substituted with $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, are either commercially available or can be prepared from compounds of formula XV, in which R_{14} is a nitrogen protecting group, such as trifluoromethyl acetyl, or more preferably acetyl, R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-SO_2NR_6R_7$, by reaction with either aqueous base or aqueous acid. These reactions are typically performed in a protic solvent such as water, methyl alcohol, ethyl alcohol or a mixture thereof, and at temperatures ranging from 25 °C to 100 °C, preferably 60-70 °C. For example, compound **465** (Scheme XII) is allowed to react with 1N aqueous hydrochloric acid solution in ethanol at reflux temperature to afford **466.**



XV

Scheme XII

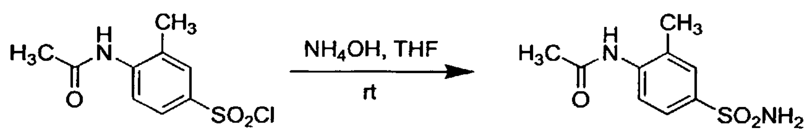


465 466

Compounds of formula V, in which R_3 is hydrogen and R_4 is C_{6-14}aryl substituted with $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, can be prepared from compounds of formula XV, in which R_{14} is a nitrogen protecting group, such as trifluoromethyl acetyl, or more preferably acetyl, R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1}-

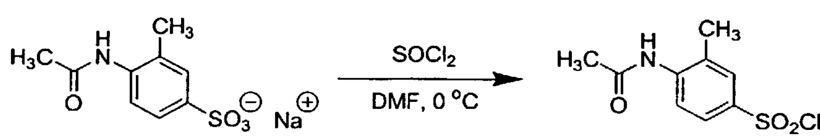
$_8$alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-SO_2Cl$, by reaction with an appropriate amine. These reactions are typically conducted in a solvent such as ethyl alcohol, THF or acetone and at temperatures from -10 °C to 50 °C, preferably 20-25 °C. For example, sulfonyl chloride **464** (Scheme XIII) is allowed to react with ammonium hydroxide in THF at ambient temperature to afford sulfonamide **465**.

Scheme XIII



Compounds of formula XV, in which R_{14} is a nitrogen protecting group, such as trifluoromethyl acetyl, or more preferably acetyl, R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-SO_2Cl$, can be prepared from compounds of formula XV, in which R_{16} is $-SO_3H$ or a salt thereof, by reaction with an agent capable of converting a sulfonic acid or a salt thereof to a sulfonyl chloride. Among the agents that are capable of affecting this transformation are phosphorous oxychloride ($POCl_3$), or thionyl chloride. These reactions are conducted in an aprotic solvent such as DMF, and at temperatures from -10 °C to 100 °C, preferably 0 °C. For example, compound **463** (Scheme XIV) is allowed to react with thionyl chloride in DMF at 0 °C to provide sulfonyl chloride **464**.

Scheme XIV

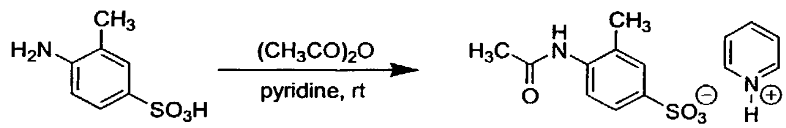


463 **464**

Compounds of formula XV, in which R_{14} is a nitrogen protecting group, such as trifluoromethyl acetyl, or more preferably acetyl, R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-SO_3H$ or a salt thereof, can be prepared from compounds of formula XV, in which R_{14} is hydrogen, by reaction with an agent capable of selectively protecting the amino group. Among the reagents that are capable of affecting this transformation are trifluoroacetic anhydride, acetyl chloride, or more preferably acetic anhydride. These reactions are conducted in an aprotic solvent, such as acetonitrile, dichloromethane, chloroform, or more preferably pyridine, and at

temperatures from 0 °C to 100 °C, preferably ambient temperatures. For example, 2-aminotoluene-5-sulfonic acid (Scheme XV) is allowed to react with acetic anhydride in pyridine at ambient temperature to provide compound **462**.

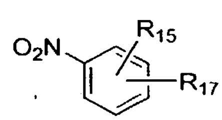
Scheme XV



462

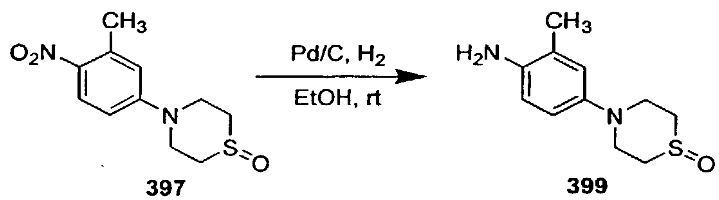
Compounds of formula XV, in which R_{14} is hydrogen, R_{15} is hydrogen, halogen, C_{1-8}-alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-SO_3H$ or a salt thereof, are commercially available or can be prepared by literature methods familiar to those skilled in the art.

Compounds of formula V in which R_3 is hydrogen and R_4 is C_{6-14}arylheterocycle substituted with $-SO_2$, -S(O), or C(O), can be prepared from compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{17} is a heterocycle substituted with $-SO_2$, -S(O), or C(O), by reaction with an agent or a combination of agents capable of selectively reducing the nitro group to an amino group. Among the agents capable of affecting this transformation are palladium on carbon in combination with hydrogen gas, Raney nickel in combination with hydrogen gas, iron in combination with hydrochloric acid, or tin (II) chloride in combination with hydrochloric acid. These reactions are typically performed in a protic solvent such as water, methyl alcohol, ethyl alcohol or a mixture thereof, and at temperatures ranging from ambient to 100 °C, preferably 40-85 °C. For example, compound **397** (Scheme XVI) is allowed to react with palladium on carbon in combination with hydrogen gas in ethyl alcohol at ambient temperature to afford compound **399**.



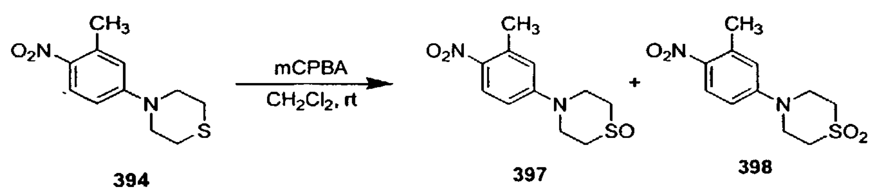
XVI

Scheme XVI



Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{17} is a heterocycle substituted with $-SO_2$, or -S(O), can be prepared from compounds of formula XVI in which R_{17} is a heterocycle substituted with -S, by reaction with an agent capable of oxidizing a sulfide to a sulfoxide or a sulfone. Among the agents capable of affecting this transformation are meta-chloroperbenzoic acid (mCPBA), hydrogen peroxide, or oxone. These reactions are typically performed in solvents such as water, THF, acetonitrile, dichloromethane, methyl alcohol, ethyl alcohol, or a mixture thereof and at temperatures from 0 °C to 100 °C. For example, compound **394** (Scheme XVII) is allowed to react with MCPBA in chloroform at room temperature to provide both the sulfoxide **397** and the sulfone **398**.

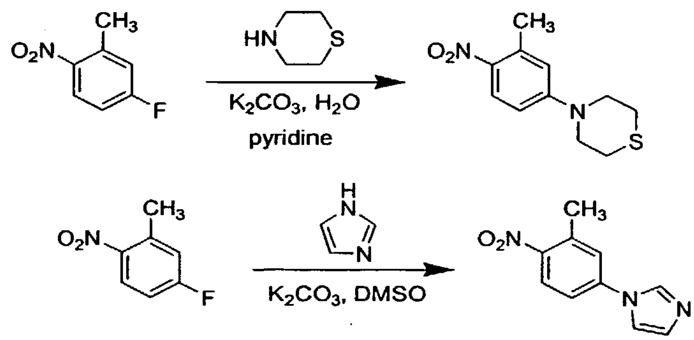
Scheme XVII



Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{17} is a heterocycle substituted with -S, or -O can be prepared from compounds of formula XVI, in which R_{17} is or contains a suitable leaving group, such as a halide, preferably fluorine, chlorine, or bromine, by reaction with heterocyclic compounds capable of displacing the leaving group. Among the heterocycles that can affect this transformation are imidazole, 1,2,3-triazole, 1,2,4-triazole, morpholine, thiomorpholine, N-methylpiperazine, piperazine, and piperidine. These reactions are typically performed in an aprotic solvent such as dioxane, THF, dimethylsulfoxide or pyridine, and in the presence of a base such as triethylamine, or more preferably sodium or potassium carbonate, and at temperatures from 0 °C to 150 °C, preferably 50-100 °C. Two such examples are shown below in Scheme XIX. In the first example, 5-fluoro-2-nitrotoluene is allowed to react with thiomorpholine in pyridine and water and in the presence of potassium carbonate to afford compound X. In the second example, 5-fluoro-

2-nitrotoluene is allowed to react with imidazole in dimethylsulfoxide, in the presence of potassium carbonate, at 70 °C to provide compound **394**.

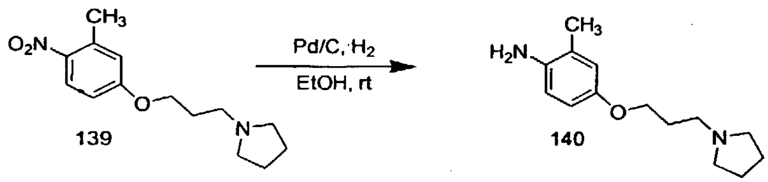
Scheme XIX



The desired heterocycles, such as those used in the schemes above, are either commercially available or can be prepared using literature methods familiar to those skilled in the art.

Compounds of formula XV, in which R_{14} is hydrogen, R_{15} is hydrogen, halogen, C_{1-8}-alkyl, C_{1-8}alkoxy, nitro, nitrile, or trifluoromethyl, and R_{16} is $-OR_8$, wherein R_8 is C_{1-8}alkyl, optionally substituted with C_{1-8}alkoxide, alkylamine, $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, or heterocycle can be prepared from compounds of formula XVI in which R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-OR_8$, by reaction with agents or a combination of agents which are capable of selectively reducing the nitro group to an amino group. Among the agents capable of affecting this transformation are palladium on carbon in combination with hydrogen gas, Raney nickel in combination with hydrogen gas, iron in combination with hydrochloric acid, or tin (II) chloride in combination with hydrochloric acid. These reactions are typically performed in a protic solvent such as water, methyl alcohol, ethyl alcohol or a mixture thereof, and at temperatures ranging from ambient to 100 °C, preferably 40-85 °C. For example, compound **139** (Scheme XX) is allowed to react with palladium on carbon in ethyl alcohol and in the presence of pressurized hydrogen gas to afford amine **140**.

Scheme XX



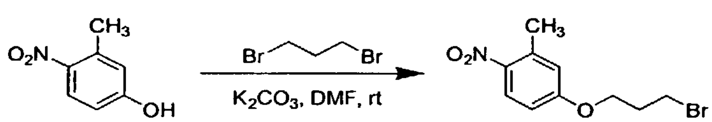
139 140

Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is -OR_8, wherein R_8 is R_8 is C_{1-8}alkyl, optionally substituted with C_{1-8}alkoxide, alkylamine, -$SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, or heterocycle can be prepared from compounds of formula XVI, in which R_{17} is hydroxy, by reaction with compounds of formula XVII in which R_{18} is C_{1-8}alkyl optionally substituted with C_{1-8}alkoxide, -$SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, or heterocycle, and R_{19} is a leaving group, preferably bromine or chlorine. These reactions are usually conducted in an aprotic solvent such as DMF, N-methylpyrrolidine, acetonitrile, or pyridine. In addition, the presence of a base such as triethylamine, or more preferably sodium or potassium carbonate is usually required. For example, 4-nitro-3-methylphenol (Scheme XXI) is allowed to react with 1,3-dibromopropane in DMF and in the presence of potassium carbonate to afford compound **249**.

$R_{19}-R_{18}$

XVII

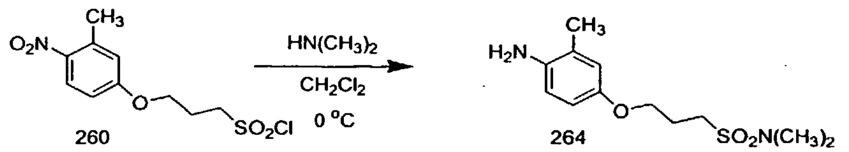
Scheme XXI



249

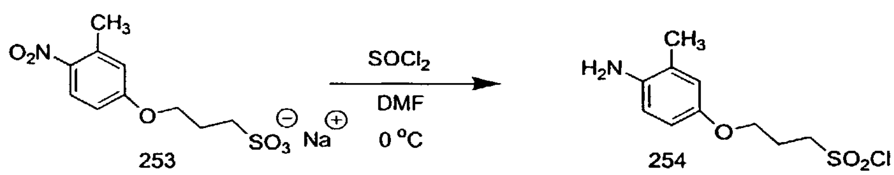
Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is -OR_8, wherein R_8 is C_{1-8}alkyl substituted with -$SO_2NR_6R_7$, can be prepared from compounds of formula XVI, in which R_8 is C_{1-8}alkyl substituted with -SO_2Cl, by reaction with ammonia or an appropriate amine. These reactions are typically performed in aprotic solvents such as acetonitrile, or more preferably dichloromethane or chloroform. For example, sulfonyl chloride **260** (Scheme XXII) is allowed to react with dimethylamine in dichloromethane at 0 °C to provide sulfonamide **264**.

Scheme XXII



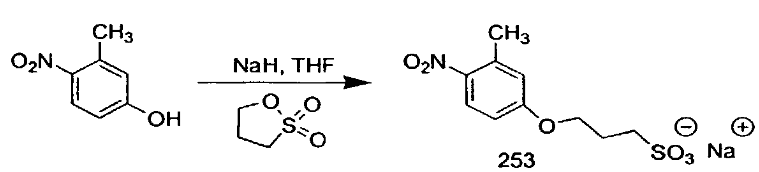
Compounds of formula XVI in which R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-OR_8$, wherein R_8 is C_{1-8}alkyl substituted with $-SO_2Cl$, can be prepared from compounds of formula XVI in which R_{17} is $-OR_8$ and R_8 is C_{1-8}alkyl substituted with $-SO_3H$ or a salt thereof, by reaction with an agent capable of converting a sulfonic acid or a salt thereof to a sulfonyl chloride. Among the agents capable of affecting this transformation are $POCl_3$, or more preferably thionyl chloride. These reactions are typically performed in an aprotic solvent such as dichloromethane, chloroform, or DMF. For example, compound **253** (Scheme XXIII) is allowed to react with thionyl chloride in DMF at 0 °C to afford sulfonyl chloride **254**.

Scheme XXIII



Compounds of formula XVI, in which R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-OR_8$, wherein R_8 is C_{1-8}alkyl substituted with $-SO_3H$ or a salt thereof, can be prepared from compounds of formula XVI, in which R_{17} is $-OR_8$, wherein R_8 is hydrogen, by reaction with a cyclic sulfonate ester, more commonly known as a sultone. These reactions are conducted in an aprotic solvent, such as DMF, acetonitrile, acetone, or more preferably THF and in the presence of a base such as potassium carbonate, or more preferably sodium hydride. For example, 3-methyl-4-nitrophenol (Scheme XXIV) is allowed to react with 1,3-propane sultone in THF and in the presence of sodium hydride to afford sulfonic acid salt **253**.

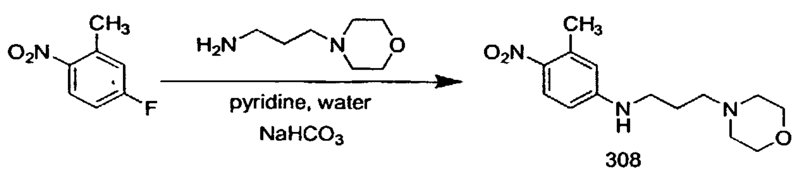
Scheme XXIV



The desired sultones, such as 1,3-propane sultone, are either commercially available or can be prepared by literature methods familiar to those skilled in the art.

Compounds of formula XVI, wherein R_{15} is hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, or trifluoromethyl, and R_{17} is $-NR_6R_7$, can be prepared from compounds of formula XVI, in which R_{17} is a suitable leaving group such as a halide, preferably chlorine or fluorine, by reaction with an appropriate amine. These reactions are conducted in solvents such as DMF, acetonitrile, dioxane, water, pyridine, or a mixture thereof, and in the presence of a base such as sodium or potassium carbonate, or more preferably sodium bicarbonate. For example, 5-fluoro-2-nitrotoluene (Scheme XXV) is allowed to react with 4-(3-aminopropyl)morpholine in pyridine and water and in the presence of sodium bicarbonate to provide compound **308**.

Scheme XXV



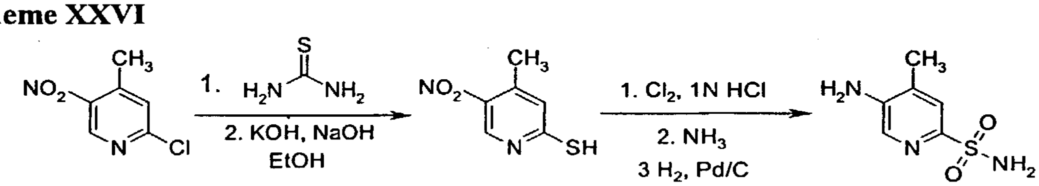
The desired amines of formula HNR_6R_7 are either commercially available or can be prepared using literature methods known in the art.

Compounds of formula V, in which R_3 is hydrogen and R_4 is an aromatic heterocycle, are either commercially available or can be prepared using literature methods familiar to those skilled in the art.

Compounds of formula (V) in which R_3 is hydrogen and R_4 is heterocycle, pyridine for example, substituted with $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, can be prepared by the methods shown below or by methods known to those skilled in the art. For example, 5-amino-4-methyl-2-pyridinesulfonamide can be prepared from 2-chloro-4-methyl-5-nitropyridine as shown in scheme XXVI. Commercially available 2-chloro-4-methyl-5-nitropyridine is allowed to react with an agent capable of displacing the 2-chloro group with a sulfur atom to provide 4-methyl-5-nitro-2-pyridinethiol, for example, thiourea. These reactions are typically performed in a polar, protic solvent, acetic acid, for example and in the presence of a base, potassium and sodium hydroxide for example, and at temperatures from 20 °C to 150 °C. The resulting thiol is then allowed to react with a reagent capable of oxidizing the thiol to the sulfonic acid derivative, for example hydrogen

peroxide, oxone or chlorine gas. The oxidation can be advantageously performed using chlorine gas as the oxidizing agent in an acidic solvent, 1N hydrochloric acid for example, with the concomitant formation of the corresponding, desired sulfonyl chloride. The resulting sulfonyl chloride is then allowed to react with an agent capable of converting it to the corresponding sulfonamide, ammonia gas or a solution of ammonia in an appropriate solvent such as dichloromethane, to provide 4-methyl-5-nitro-2-pyridinesulfonamide. The nitro group can then be reduced using methods known to those skilled in the art, palladium on carbon in the presence of hydrogen gas as the reducing agent for example, to produce the desired 5-amino-4-methyl-2-pyridinesulfonamide. The reduction reactions are typically performed in a polar, protic solvent, methanol for example, and at temperatures from 20 °C to 100 °C, preferably at ambient temperature.

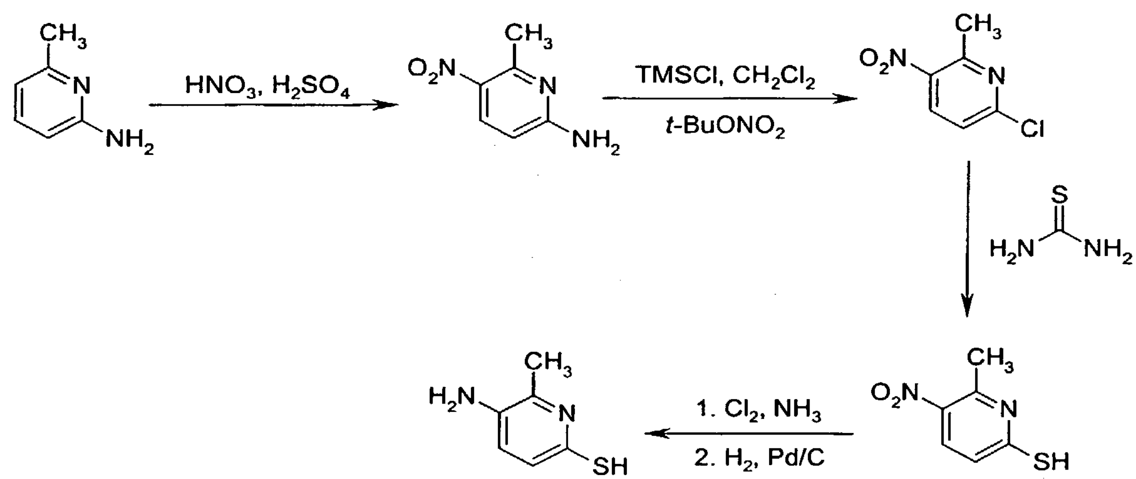
Scheme XXVI



Alternatively, compounds of formula (V), in which R_3 is hydrogen and R_4 is heterocycle, pyridine for example, substituted with $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, can be prepared by the methods shown below or by methods known to those skilled in the art. For example, 5-amino-6-methyl-2-pyridinesulfonamide can be prepared as shown in scheme XXVII. Commercially available 2-amino-5-methylpyridine is allowed to react with an agent capable of nitrating the pyridine ring, for example a mixture of nitric and sulfuric acids. These reactions are typically performed in concentrated sulfuric acid as solvent, and at temperatures from –10 °C to 25 °C, preferably at 0 °C, to produce the desired 5-amino-2-methyl-3-nitropyridine. The amino group is then allowed to react with a combination of agents capable of converting the amino group to a chlorine substituent. For example, 5-amino-2-methyl-3-nitropyridine was allowed to react with tert-butylnitrite, to produce the corresponding diazonium salt, followed by reaction with trimethylsilyl chloride in an aprotic solvent, dichloromethane for example, to afford 5-chloro-2-methyl-3-nitropyridine. The chloro group is then allowed to react with an agent capable of effecting a substitution on the pyridine ring to produce the corresponding thiol derivative. For example, 5-chloro-2-methyl-3-nitropyridine was allowed to react with thiourea in a mixture of acetic acid, potassium hydroxide and sodium hydroxide to afford

the desired 6-methyl-5-nitro-2-pyridinethiol. The resulting thiol is then allowed to react with a reagent capable of oxidizing the thiol to the sulfonic acid derivative, for example hydrogen peroxide, oxone or chlorine gas. The oxidation can be advantageously performed using chlorine gas as the oxidizing agent in an acidic solvent, 1N hydrochloric acid for example, with the concomitant formation of the corresponding, desired sulfonyl chloride. The resulting sulfonyl chloride is then allowed to react with an agent capable of converting it to the corresponding sulfonamide, ammonia gas or a solution of ammonia in an appropriate solvent such as dichloromethane, to provide 6-methyl-5-nitro-2-pyridinesulfonamide. The nitro group can then be reduced using methods known to those skilled in the art, palladium on carbon in the presence of hydrogen gas as the reducing agent for example, to produce the desired 5-amino-6-methyl-2-pyridinesulfonamide. The reduction reactions are typically performed in a polar, protic solvent, methanol for example, and at temperatures from 20 °C to 100 °C, preferably at ambient temperature.

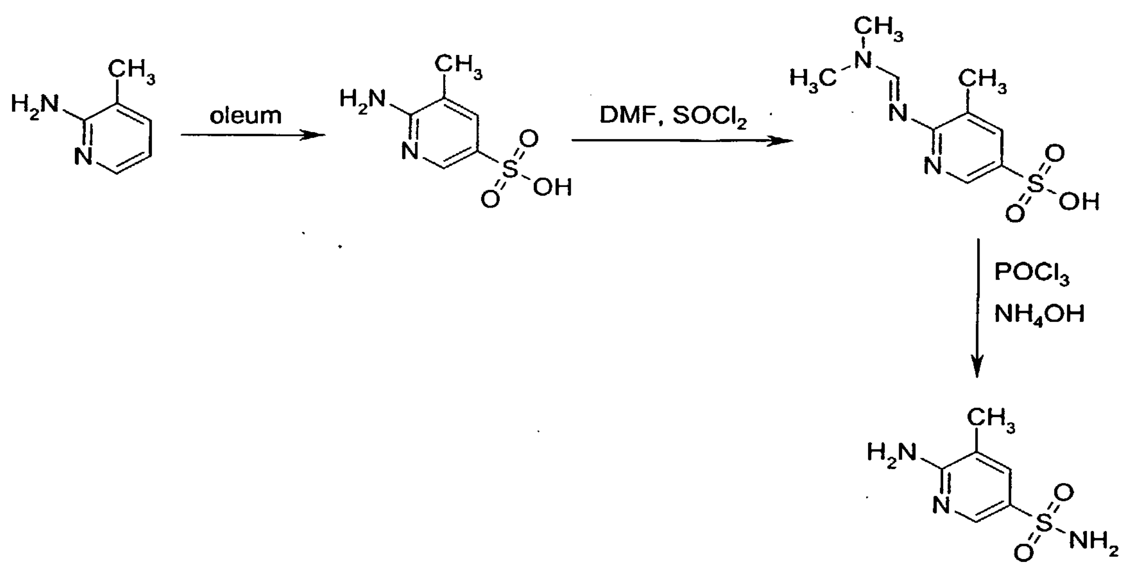
Scheme XXVII



Alternatively, compounds of formula (V) in which R_3 is hydrogen and R_4 is heterocycle, pyridine for example, substituted with $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, can be prepared by the methods shown below or by methods known to those skilled in the art. For example, 6-amino-5-methyl-3-pyridinesulfonamide can be prepared as shown in scheme XXVIII. Commercially available 2-amino-3-methylpyridine is allowed to react with an agent capable of sulfonylating the pyridine ring, for example oleum. These reactions are typically performed in a mixture of 20%SO3/H2SO4, at

temperatures ranging from 75 °C to 200 °C, preferably 160°C, to produce 6-amino-5-methyl-3-pyridinesulfonic acid. The amino group is then allowed to react with a combination of agents capable of effecting protection of the amino group from oxidation in subsequent steps. For example, 6-amino-5-methyl-3-pyridinesulfonic acid was allowed to react with a mixture of N,N-dimethylformamide (DMF) and thionyl chloride, so-called Vilsmier reagents, to produce the desired 6-[(dimethylamino)methylidene]amino-5-methyl-3-pyridinesulfonic acid intermediate. This compound is then allowed to react with a combination of agents capable of converting the sulfonic acid to the corresponding sulfonyl chloride, followed by reaction with an agent capable of converting the sulfonyl chloride to the corresponding sulfonamide derivative. For example, desired 6-[(dimethylamino)methylidene]amino-5-methyl-3-pyridinesulfonic acid is allowed to react with phosphorous oxychloride to produce the intermediate sulfonyl chloride, followed by reaction with ammonium hydroxide, to afford the desired 6-amino-5-methyl-3-pyridinesulfonamide.

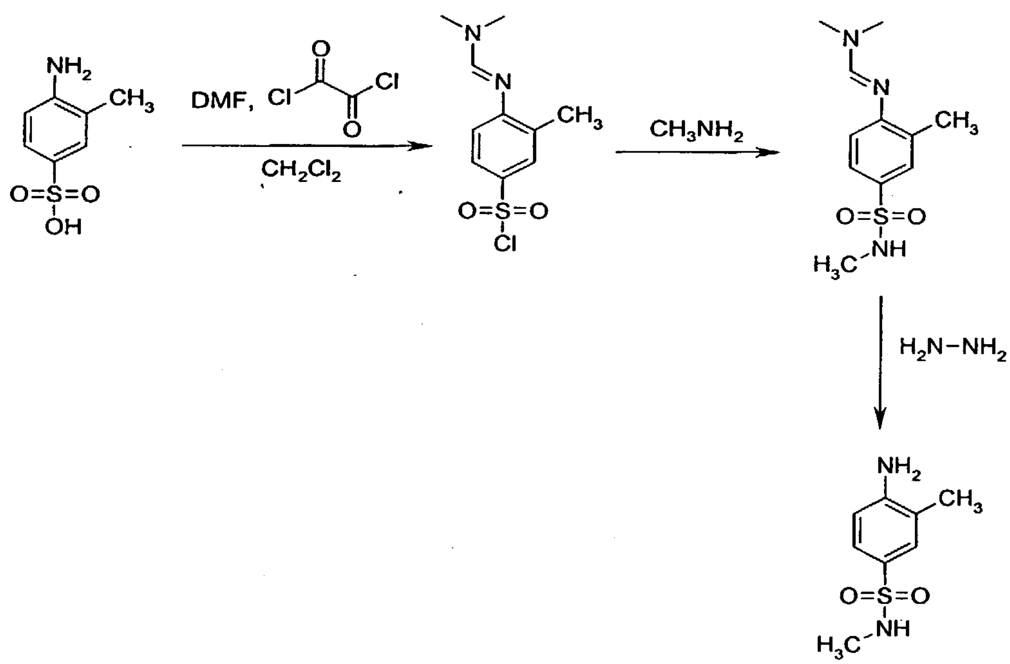
Scheme XXVIII



Compounds of formula (XV) wherein R_{14} is hydrogen, R_{15} is hydrogen halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, can be prepared by methods known in the art or by the method shown in Scheme XXIX. For example, 4-amino-*N*,3-dimethylbenzenesulfonamide can be prepared from commercially available 4-amino-3-methylbenzenesulfonic acid by

reaction with a combination of reagents capable of effecting protection of the amino group from oxidation in later chemical steps. For example, 4-amino-3-methylbenzenesulfonic acid was allowed to react with N,N-dimethylformamide (DMF) and oxalyl chloride in dichloromethane to effect the concomitant protection of the amino group as the corresponding amidine as well as converting the sulfonic acid to the desired sulfonyl chloride. The sulfonyl chloride was then allowed to react with an amine, methyl amine for example, to produce 4-[(dimethylamino)methylidene]amino-*N*,3-dimethylbenzenesulfonamide. The amidine-protecting group was then removed using hydrazine hydrochloride.

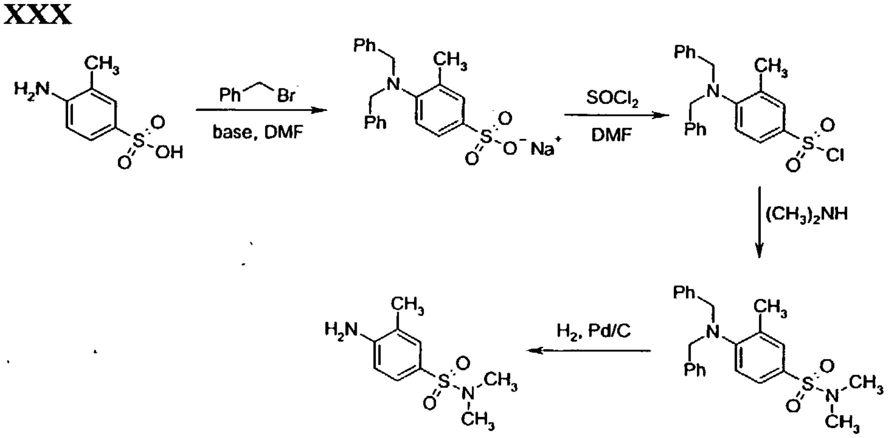
Scheme XXIX



Alternatively, compounds of formula (XV), wherein R_{14} is hydrogen, R_{15} is hydrogen halogen, C_{1-8}alkyl, C_{1-8}alkoxy, nitro, nitrile, trifluoromethyl, and R_{16} is $-SO_2NR_6R_7$, wherein R_6 and R_7 are as hereinbefore defined, can be prepared by methods known in the art or by the method shown in Scheme XXX. For example, 4-amino-*N*,*N*,3-trimethylbenzenesulfonamide can be prepared by methods known in the art or as shown in Scheme XXX. Commercially available 4-amino-3-methylbenzenesulfonic acid is allowed to react with an agent capable of effecting protection of the amino group from oxidation in further synthetic steps. For example, 4-amino-3-methylbenzenesulfonic acid was allowed

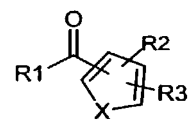
to react with benzyl bromide in the presence of a base, sodium or potassium carbonate for example, to afford sodium 4-(dibenzylamino)-3-methylbenzenesulfonate. These reactions are typically performed a polar, aprotic solvent, N,N-dimethylformamide for example, at temperature ranges from 25 °C to 125 °C, preferably 75-100 °C. The sodium salt is then allowed to react with an agent capable of converting the salt to the corresponding sulfonyl chloride. For example, afford sodium 4-(dibenzylamino)-3-methylbenzenesulfonate was allowed to react with thionyl chloride in N,N-dimethylformamide (DMF) to afford the desired 4-(dibenzylamino)-3-methylbenzenesulfonyl chloride. These reactions are typically performed in an aprotic solvent, dichloromethane for example, and at temperatures from 0 °C to 75 °C, preferably 0 °C. The sulfonyl chloride is then allowed to react with an appropriate amine to afford the desired sulfonamide. For example, 4-(dibenzylamino)-3-methylbenzenesulfonyl chloride was allowed to react with dimethylamine to afford the desired 4-(dibenzylamino)-*N*,*N*,3-trimethylbenzenesulfonamide. The sulfonamide is then allowed to react with a combination of agent capable of effecting the deprotection of the amine to produce the desired aniline derivative. For example, desired 4-(dibenzylamino)-*N*,*N*,3-trimethylbenzenesulfonamide was allowed to react with hydrogen gas in the presence of a palladium on carbon catalyst to effect cleavage of the benzyl protecting groups and afford the desired 4-amino-*N*,*N*,3-trimethylbenzenesulfonamide.

Scheme XXX

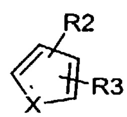


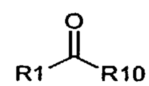
Compounds of formula XVIII where R_2 is either a hydroxy or methoxy group and R_1 and R_3 are as hereinbefore defined, and X is a heteroatom, preferably oxygen or sulfur, can be prepared from compounds of formula XIX with compounds of formula X where R_1 is hereinbefore defined and R_{10} is a halogen, preferably chlorine, with the stipulation that

R_1 and R_3 are chemically compatible with the reaction conditions and that R_2, R_3 and R_1CO are regiochemically compatible in such reactions. These reactions, typically called Friedel-Craft acylations, are performed according to processes previously described (see, for example, Scheme X). For example, 3-methoxythiophene (Scheme XXXI) is allowed to react with benzoyl chloride in refluxing dichloromethane in the presence of aluminum chloride to afford ketone **664**.



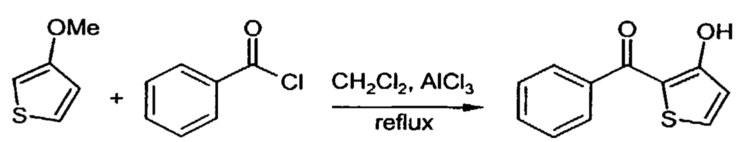
XVIII





XIX X

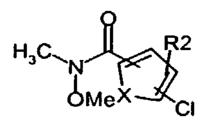
Scheme XXXI



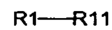
664

Compounds of formula XVIII where R_1 and R_3 are as hereinbefore defined and R_2 is methoxy and X is a heteroatom, preferably sulfur or oxygen, can be prepared from the reaction of compounds of formula XX in which R_2 and R_3 are as hereinbefore defined with compounds of XIII in which R_1 is as hereinbefore defined, and R_{11} is a halogen, preferably bromine or iodine, with the stipulation that R_1 and R_5 are chemically compatible with subsequent chemical steps and that the N,O-dimethylhydroxyacetamide, R_2 and R_3 groups

are regiochemically compatible in such a reaction. Typically, conditions for such reactions are similar to those described for the synthesis of compounds of formula XII.



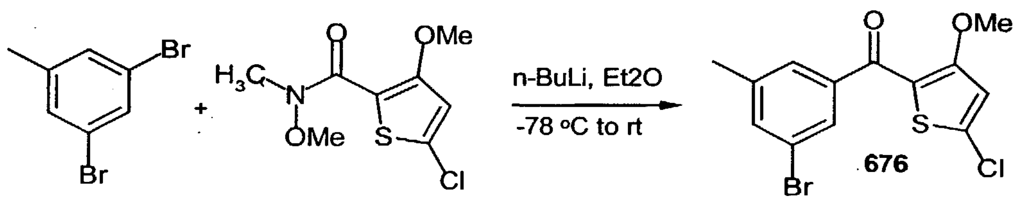
XX



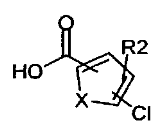
XIII

For example, 3,5-dibromotoluene in diethyl ether was treated with n-butyllithium at -78 °C. After 15 minutes at -78 °C, the resulting lithium species is allowed to react with **675** to afford the desired ketone **676** (see Scheme XXXIII).

Scheme XXXIII



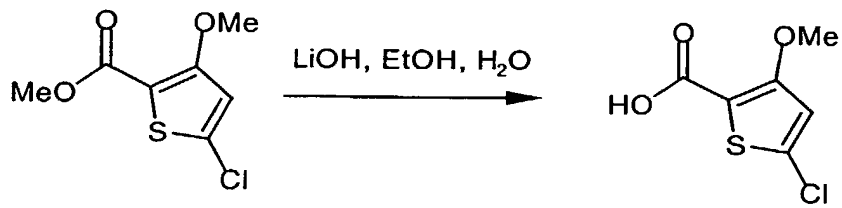
Finally, compounds of formula XX can be prepared from compounds of formula XXI where R_2 and R_3 are as hereinbefore defined using procedures previously described for the synthesis of compounds of formula X (See Scheme VII).



XXI

Compounds of formula XXI can, in turn, be prepared according to procedures described in the literature. See for example *Synthesis*, **1984**, 847 for the synthesis of **673** which after hydrolysis provided compound **674** (Scheme XXXIV).

Scheme XXXIV



673 **674**

A further object of the present invention features intermediates **7, 32, 33, 36, 38, 44, 45, 49, 51, 52, 61, 65, 66, 71, 75, 76, 111, 112, 115, 118, 119, 128, 129, 171, 172, 191, 192, 199, 200, 206, 207, 224, 225, 232, 233, 235, 236, 246, 247, 253, 254, 255, 256, 259, 260, 261, 262, 264, 265, 267, 268, 288, 289, 290, 409, 412, 428, 430, 431, 433, 477, 490, 495, 496, 507, 511, 514, 515, 518, 519, 522, 523, 526, 527, 529, 530, 532, 533, 537, 538, 540, 541, 543, 544, 546, 553, 556, 558, 559, 561, 562, 567, 568, 572, 573, 576, 577, 582, 584, 585, 588, 589, 595, 602, 603, 608, 611, 612, 616, 620, 621, 638, 639, 648, 653, 661, 662, 671, 676, 677** useful in the manufacture of the compounds of the present invention.

The compounds according to the invention, also referred to herein as the active ingredient, may be administered for therapy by any suitable route including oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and intravitreal). It will be appreciated that the preferred route will vary with the condition and age of the recipient, the nature of the infection and the chosen active ingredient.

In general a suitable dose for each of the above-mentioned conditions will be in the range of 0.01 to 250 mg per kilogram body weight of the recipient (e.g. a human) per day, preferably in the range of 0.1 to 100 mg per kilogram body weight per day and most preferably in the range 0.5 to 30 mg per kilogram body weight per day and particularly in the range 1.0 to 20 mg per kilogram body weight per day. Unless otherwise indicated, all weights of active ingredient are calculated as the parent compound of formula (I); for salts or esters thereof, the weights would be increased proportionally. The desired dose may be presented as one, two, three, four, five, six or more sub-doses administered at appropriate

intervals throughout the day. In some cases the desired dose may be given on alternative days. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1000 mg or 50 to 500 mg, preferably 20 to 500 mg, and most preferably 100 to 400 mg of active ingredient per unit dosage form.

While it is possible for the active ingredient to be administered alone it is preferable to present it as a pharmaceutical formulation. The formulations of the present invention comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof and optionally other therapeutic agents. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and intravitreal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

The present invention further includes a pharmaceutical formulation as hereinbefore defined wherein a compound of formula (I) or a pharmaceutically acceptable derivative thereof and at least one further therapeutic agent are presented separately from one another as a kit of parts.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3)

dispersed in a polymer. A suitable concentration of the active compound is about 1% to 25%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis as generally described in *Pharmaceutical Research* 3 (6), 318 (1986).

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Formulations suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral

administration may include such further agents as sweeteners, thickeners and flavoring agents.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way. "Active ingredient" denotes a compound according to the invention or multiples thereof or a physiologically functional derivative of any of the aforementioned compounds.

General Procedures:

General procedure I: Friedel-Crafts reaction of acid chlorides with 4-chloroanisole

Into a round-bottom flask equipped with a stir bar, a reflux condenser, and nitrogen on demand, were placed 4-chloroanisole (1-1.25 mmol/mmol of acid chloride), aluminum chloride ($AlCl_3$, 1-1.75 mmol/mmol of acid chloride) and CH_2Cl_2. To the resulting mixture was added the appropriate acid chloride at rt. When the addition was complete, the orange mixture was heated to reflux and was allowed to stir for 2-24 h. The mixture was allowed to cool to rt and was carefully poured onto ice water, giving a two-phase mixture which was stirred at rt for 30 min to 2 h. It was then poured into a separatory funnel containing water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. See specific examples for details regarding additional purification.

General procedure II: Alkylation of phenols with ethyl bromoacetate

Into a round-bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand were placed the appropriate phenol, potassium carbonate (2-10 mmol/mmol of phenol), ethyl bromoacetate (1-1.5 mmol/mmol of phenol) and acetone (1-10 mL/mmol of phenol). The resulting mixture was heated to reflux for 1-20 h, after which time it was allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to leave an oil. See specific examples for details regarding additional purification.

General procedure III: Saponification of ethyl esters to the carboxylic acids

A round-bottom flask was equipped with a stir bar, nitrogen on demand and was flushed with nitrogen. To the flask were added tetrahydrofuran (THF, 1-5 mL/mmol of ester), ethyl alcohol (EtOH, 1-5 mL/mmol of ester), water (1-5 mL/mmol of ester) and lithium hydroxide monohydrate (1-5 mmol/mmol of ester). The resulting suspension was stirred vigorously and the ester was added in one portion. The mixture was allowed to stir at rt for 1-20 h, after which time the pH was adjusted to approximately pH 5 by the slow addition of 1 N aqueous hydrochloric acid. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to leave a white solid. See specific examples to determine if further purification of the product was required.

General procedure IV: Coupling of the acid to aromatic amines using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC)

A round-bottom flask was equipped with a stir bar, nitrogen on demand and was flushed with nitrogen. To the flask were added the appropriate carboxylic acid, N,N-dimethylformamide (DMF, 5-20 mL/mmol acid), 1-hydroxybenztriazole (HOBt, 1-2 mmol/mmol acid), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC, 1-5 mmol/mmol acid), and the appropriate aromatic amine (1-2 mmol/mmol acid). In some cases, triethylamine (Et_3N, 2-5 mmol/mmol of acid) was used. The resulting mixture was allowed to stir at rt for 2-24 h, after which time it was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. See specific examples for details regarding further purification of the products.

General Procedure V: Synthesis of acid chlorides from carboxylic acids using oxalyl chloride

Into a round-bottom flask were placed the appropriate carboxylic acid, methylene chloride (CH_2Cl_2, 1-10 mL/mmol acid), and N,N-dimethylformamide (1-10 drops). The mixture was cooled to 0 °C and oxalyl chloride (1-2 mmol/mmol acid) was added dropwise, after

which time the mixture was allowed to warm to rt and stir for 1-24 h. The solvents were then removed under reduced pressure and the remaining residue was dried in vacuo. In most cases, the acid chlorides were used immediately used in subsequent reactions with no further purification.

General procedure VI: Coupling of acid chlorides to aromatic amines using sodium bicarbonate

Into a round-bottom flask were placed the appropriate aromatic amine, acetone (1-10 mL/mmol amine), sodium bicarbonate (2-10 mmol/mmol amine), and water (0.25-10 mL). The acid chloride was added as a solution in acetone (1-10 mL/mmol of acid chloride) in a dropwise manner and the reaction mixture was allowed to stir at rt for 1-24 h. When judged to be complete, the mixture was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. See specific examples for details regarding further purification of the products.

General procedure VII: Synthesis of Weinreb amides from acid chlorides using N,O-dimethylhydroxylamine hydrochloride

Into a round bottom flask equipped with a stir bar and nitrogen on demand were placed the N,O-dimethylhydroxylamine (1-2 mmol/mmol acid chloride) and chloroform ($CHCl_3$, 1-10 mL/mmol acid chloride). The mixture was cooled to 0 °C and triethylamine (Et_3N, 1-5 mmol/mmol acid chloride) was added in one portion. The acid chloride was added and the reaction mixture was allowed to stir at 0 °C for 0.5-5 h, after which time was poured into a separatory funnel containing chloroform and water. The organics were collected, washed with water and brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. See specific examples to determine if further purification of the product was required.

General procedure VIII: Halogen-metal exchange of 2-bromo-4-chloroanisole, followed by addition of Weinreb amides

Into a round-bottom flask equipped with a stir bar, nitrogen on demand, and an addition funnel, were added 2-bromo-4-chloroanisole (1 mmol/mmol of amide) and diethyl ether (1-10 mL/mmol of anisole) and the mixture was cooled to –78 °C by means of a dry ice/acetone bath. N-Butyl lithium (1-2 mmol/mmol of anisole of a 2.5M soln. in hexanes) was added dropwise, followed by addition of the Weinreb amide. The reaction was allowed to stir at -78 °C for 0.5h-1h, at which time the reaction was allowed to warm to rt. When judged to be complete, the reaction was poured into a separatory funnel containing ether and water. The organics were collected, washed with water, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. See specific examples to determine if further purification was required.

General procedure IX: Deprotection of anisole derivatives using boron tribromide

To a round-bottom flask equipped with a stir bar, nitrogen on demand, and an addition funnel was added the appropriate anisole derivative and methylene chloride (CH_2Cl_2, 1-15 mL/mmol of anisole). The mixture was cooled to –78 °C and boron tribromide was added dropwise at –78 °C. The resulting mixture was allowed to stir at –78 °C for 30-120 minutes, after which time it was allowed to warm to rt and stir for an additional 15-120 minutes. When judged to be complete, the reaction was poured over ice and extracted with CH_2Cl_2. The organics were collected, washed with water, dried over $MgSO_4$, filtered, and the solvents were removed. See specific examples to determine if further purification was required.

General Procedure X. The appropriate acid chloride in acetonitrile was added dropwise via an addition funnel to a stirred solution of triethylamine (0-2.5mmol/mmol acid chloride), acetonitrile (1-20 ml/mmol acid chloride), and the appropriate aniline (0.5-2.5 mmol/mmol acid chloride). The reaction was refluxed for 0-12 h. The heat was removed and the reaction mixture was stirred for 12-336 h. The mixture was concentrated, dissolved, and washed with water. The resulting organics were dried over $MgSO_4$ and concentrated in vacuo and purified as descried in the individual cases.

General Procedure XI. An amine (1-2.5 mmol/mmol benzene) was added dropwise via an addition funnel to a stirred suspension of a para-nitro halogenated benzene or toluene in

pyridine (20-40 mmol/mmol benzene), sodium bicarbonate (1.5-4 mmol/mmol benzene), and water (0.2-5 mL/mmol benzene). The resulting suspension was refluxed (150 °C) for 1-7 days. The mixture was filtered and acetone (10-200 mL/mmol benzene) was added to the filtrate and brought to reflux. Water was added to the cloud point and the solution was cooled to rt. The precipitate was filtered and the resulting solid was washed with water and ether to afford the substituted product.

General Procedure XII. The appropriate nitro-benzene was added to a suspension of palladium on carbon (0.1-0.8 mmol /mmol benzene, 10% w/w), ethanol, THF, and methanol and the reaction vessel was evacuated and charged with nitrogen several times. After evacuating the reaction vessel under reduced pressure, it was charged with hydrogen (14-100 psi). The resulting suspension was stirred at rt for 0-72 h, filtered through a celite pad, and concentrated in vacuo to afford the appropriate aniline.

General procedure XIII. Into a round-bottom flask equipped with a stir bar, cooling bath, and nitrogen on demand were placed the appropriate carboxylic acid, hexachloroacetone (HCA, 0.5 mmol/mmol acid), and THF (1-10 mL/mmol acid) and the mixture was cooled -78 °C. Triphenylphosphine (PPh_3, 1 mmol/mmol acid) in THF (1-10 mL/mmol acid) was added to the mixture and stirred for 5-120 min. The appropriate aniline (1 mmol/ mmol acid) in THF (1-10 mL/mmol acid) and pyridine (5-20 mmol/mmol acid) were added dropwise and the mixture was stirred -78 °C for 5-60 min. The cooling bath was removed and the mixture was stirred at rt for 1h to 14 d. The reaction mixture was concentrated in vacuo and purified as described in the individual cases.

General procedure XIV. Thionyl chloride (1-100 mmol/mmol acid) was added to a solution of the appropriate carboxylic acid in methylene chloride (1-100 ml/mmol acid) and the resulting solution was refluxed for 1-12 h under nitrogen. The mixture was concentrated in vacuo and placed under nitrogen to afford the appropriate acid chloride.

General Procedure XV: Palladium-mediated cyanation of benzophenone derivatives

The appropriate bromobenzophenone was treated according to the procedures outlined by Anderson et al. in *J. Org. Chem.* **1998,** *63*, 8224-8228. Into a heat-dried flask, fitted with a reflux condenser, was placed the bromo- or trifluoromethylsulfonyl- benzophenone (1 eq),

tetrakis(triphenylphosphine) palladium (10-20%), copper iodide (2 eq relative to palladium), sodium cyanide (2 eq), and propionitrile (0.5-1.0 M in bromobenzophenone). The mixture was purged with N_2 for 30 min prior to use. The mixture was heated to 120 °C and stirred until TLC analysis showed complete disappearance of the starting material (1-16 h). The mixture was then cooled to rt, diluted with ethyl acetate, and filtered through silica gel, and the filtrate was concentrated in vacuo. The corresponding products were purified as described in each example..

General procedure XVI: Synthesis of *N*-[4-(aminosulfonyl)-2-methylphenyl]acetamide and *N*-[4-(alkyl and dialkyaminosulfonyl)-2-methylphenyl]acetamides

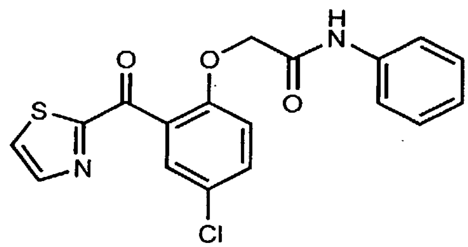
Sulfonyl chloride **464** (1-100 mmol) was added to a solution of the appropriate amine in pyridine (1-10 mL/mmol amine) and the resulting solution was stirred for 1-48 h under nitrogen. Water was added and the resulting mixture was extracted with methylene chloride and the organics were concentrated in vacuo. The resulting products were then purified by flash chromatography to afford the appropriate acetyl protected sulfonamide.

General procedure XVII:De-acetylation of *N*-[4-(aminosulfonyl)-2-methylphenyl]acetamide and *N*-[4-(alkyl and dialkyaminosulfonyl)-2-methylphenyl]acetamides

The appropriate sulfonamide (1-100 mmol) was added to a solution of ethanol (1-50 mL), water (0-5mL), and hydrochloric acid (1-28.9 M, 1-50 mL) in a large test tube. The mixture was then heated, with stirring, to 60 °C for 1-36 h. The mixture was allowed to cool to rt and concentrated in vacuo. The resulting products were dissolved in ethyl acetate and washed with saturated $NaHCO_3$, then purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford the desired aniline.

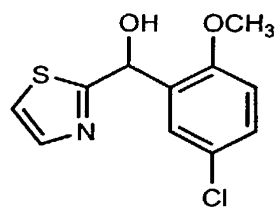
Examples:

Example 1:



1

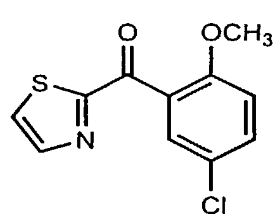
Step A:



2

A solution of 2-Bromo-4-Chloroanisole (8.98 g, 40.54 mmol) in diethyl ether (65 mL) was cooled to –78 °C and n-butyl lithium (26 mL of a 1.6 M solution in hexanes, 41.6 mmol) was added from a syringe. The resulting orange solution was allowed to stir at –78 °C for 30 min, after which time 2-thiazolecarboxaldehyde (4.53 g, 40.04 mmol) was added neat, resulting in a purple solution. The mixture was allowed to stir at -78 °C for 15 min, after which time water (50 mL) was added and the mixture was allowed to warm to RT. The mixture was poured into a separatory funnel containing ether and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a white solid. The solid was washed with hexanes and was dried in vacuo; affording white needles (5.21 g, 51%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J= 4Hz, 1H), 7.38 (d, J= 4Hz, 1H), 7.28 (d, J= 4Hz, 1H), 7.23 (m, 1H), 6.83 (d, J= 8 Hz, 1H), 6.23 (d, J= 8 Hz, 1H), 3.99 (d, J= 8Hz, 1H), 3.83 (s, 3H).

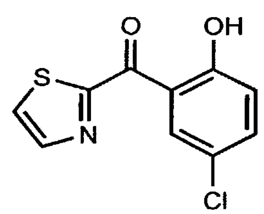
Step B:



3

2 (5.21 g, 20.6 mmol), manganese dioxide (17.66 g, 203.1 mmol) and methylene chloride (CH_2Cl_2, 75 mL) were combined under nitrogen and were allowed to stir at RT for 2.5 h. The mixture was filtered through a pad of celite, which was washed with several portions of CH_2Cl_2, and the solvent was removed under reduced pressure to provide a tan solid (4.96 g, 95%) which was used in subsequent reactions without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, J= 3 Hz, 1H), 7.76 (d, J= 3 Hz, 1H), 7.63 (d, J= 3Hz, 1H), 7.49 (dd, J= 9, 3 Hz, 1H), 7.00 (d, J= 9 Hz, 1H), 3.82 (s, 3H).

Step C:



4

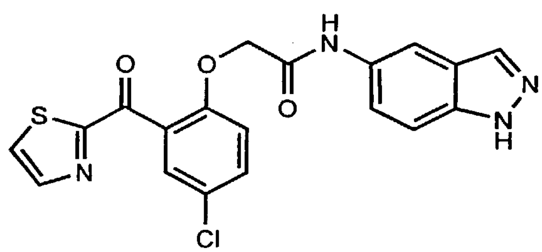
3 (4.96 g, 19.6 mmol), in CH_2Cl_2 (60 mL) was cooled to –78 °C and boron tribromide (100 mL of a 1.0 M solution in CH_2Cl_2, 100 mmol) was added via syringe over 30 min. The resulting purple solution was allowed to stir at –78 °C for 15 min, after which time it was allowed to slowly warm to RT. After 30 min at RT, the mixture was slowly poured over ice water and the resulting two-phase mixture was allowed to stir for 30 min. The mixture was then poured into a separatory funnel containing water and CH_2Cl_2. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, and the solvents were removed under reduced pressure. The product was isolated by flash chromatography using 7:3 hexane/ CH_2Cl_2 to provide a yellow solid (3.59 g, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.25 (s, 1H), 9.29 (d, J= 3 Hz, 1H), 8.19 (d, J= 3Hz, 1H), 7.83 (d, J= 3Hz, 1H), 7.53 (dd, J= 9, 3 Hz, 1H), 7.05 (d, J = 9 Hz, 1H).

Step D:

4 (0.12 g, 0.49 mmol), 2'-chloroacetanilide (0.09 g, 0.52 mmol), sodium carbonate (Na_2CO_3, 0.54 g, 5.1 mmol), potassium iodide (0.47 g, 3.1 mmol) and acetone (8 mL) were combined under nitrogen and the resulting mixture was heated to reflux. After 18 h at reflux, the mixture was allowed to cool to RT and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with

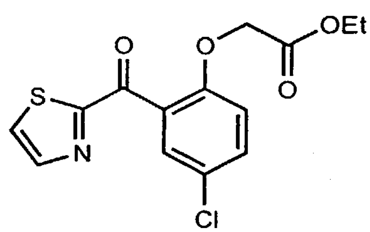
water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure, leaving orange oil. The product was isolated by flash chromatography using 4:1 hexane/ethyl acetate as eluant to provide **1** as a white solid (0.09 g, 49%). ^{1}H NMR ($CDCl_3$, 300 MHz) d 9.66 (s, 1H), 9.04 (d, J= 3 Hz, 1H), 7.93 (d, J= 2.7 Hz, 1H), 7.78 (d, J= 3Hz, 1H), 7.72 (d, J= 8Hz, 2H), 7.51 (dd, J= 3 Hz, 1H), 7.35 (m, 2H), 7.15 (m, 1H), 6.97 (d, J= 9 Hz, 1H), 4.67 (s, 2H).

Example 2:



5

Step A:



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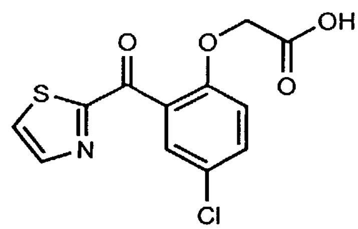
Phenol **4** (2.31 g, 9.64 mmol), K_2CO_3 (6.95 g, 50.3 mmol), ethyl bromoacetate (1.1 mL, 1.7 g, 9.9 mmol) and acetone (150 mL) were used according to general procedure II. The product was used in the next reaction without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, J= 3 Hz, 1H), 7.76 (d, J= 3 Hz, 1H), 7.66 (d, J= 3 Hz, 1H), 7.48 (dd, J= 9, 3 Hz, 1H), 6.93 (d, J= 9 Hz, 1H), 4.61 (s, 2H), 4,21 (q, J= 6 Hz, 2H), 1.26 (t, J= 6 Hz, 3H).

Step B:



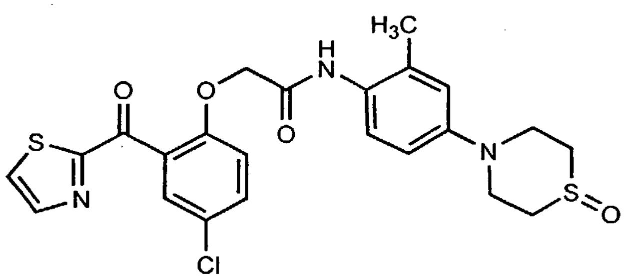
7

Ester **6** (3.1 g, 9.6 mmol), THF (30 mL), water (10 mL), EtOH (10 mL) and LiOH (1.0 g, 23.8 mmol) were used according to general procedure III. The product was used in the next reaction without any further purification. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.30 (d, J = 3Hz, 1H), 8.15 (d, J= 3 Hz, 1H), 7.63 (d, J = 3 Hz, 1H), 7.57 (dd, J= 9, 3 Hz, 1H), 7.05 (d, J= 9 Hz, 1H), 4.45 (s, 2H).

Step C:

Carboxylic acid **7** (0.1 g, 0.33 mmol), HOBt (0.05 g, 0.4 mmol), EDAC (0.09 g, 0.46 mmol), Et_3N (0.1 mL, 0.07 g, 0.72 mmol), DMF (6 mL) and 5-aminoindazole (0.05 g, 0.35 mmol) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2: CH_3OH as eluant to provide 5 as a tan solid (0.03 g, 25%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.55 (s, 1H), 8.46 (s, 1H), 8.21 (s, 1H), 8.05 (m, 2H), 7.77 (m, 3H), 7.54 (m, 1H), 6.99 (d, J= 8 Hz, 2H), 4.74 (s, 2H).

Example 3:

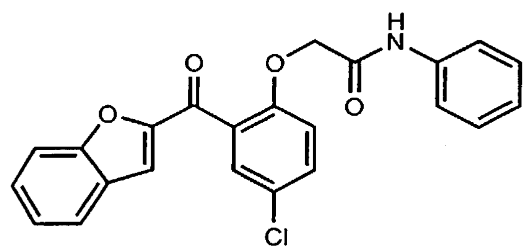


8

Carboxylic acid **7**, HOBt (0.10 g, .75 mmol), EDAC (0.15 g, 0.79 mmol), Et_3N (0.16 mL, 0.12 g, 1.15 mmol), DMF (5 mL) and sulfoxide **399** (0.15 g, 0.68 mmol) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford a tan solid (0.09 g, 34%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.14 (s, 1H), 8.00 (m, 2H), 7.80 (d, J= 3 Hz, 1H), 7.56 (m, 2H), 7.05 (d, J= 9

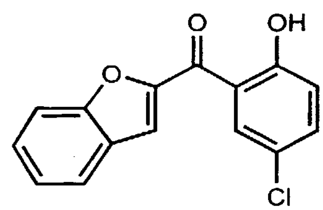
Hz, 2H), 6.87 (br s, 1H), 4.77 (s, 2H), 4.04 (m, 1H), 3.54 (m, 1H), 3.0 (m, 2H), 2.21 (s, 3H).

Example 4



9

Step A:



10

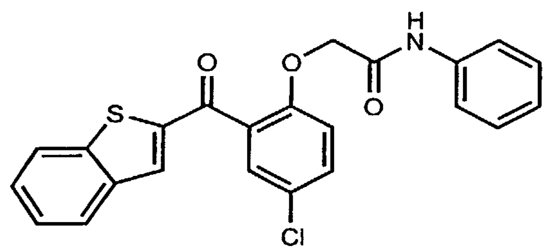
2-Benzofurancarboxylic acid (2.51 g, 15.48 mmol), CH_2Cl_2 (50 mL), DMF (4 drops), and oxalyl chloride (1.5 mL, 2.18 g, 17.19 mmol) were used to prepare the corresponding acid chloride according to general procedure V. The acid chloride was used immediately in combination with 4-chloroanisole (2.16 g, 15.15 mmol), $AlCl_3$ (3.01 g, 22.57 mmol) and CH_2Cl_2 (50 mL) according to general procedure I. Compound **10** was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide 10 as a yellow solid (2.39 g, 57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.05 (s, 1H), 8.48 (d, J= 3Hz, 1H), 7.82 (d, J= 9 Hz, 1H), 7.79 (s, 1H), 7.73 (d, J= 9 Hz, 1H), 7.56 (m, 2H), 7.42 (t, J= 7.5 Hz, 1H), 7.09 (d, J= 9 Hz, 1H).

Step B:

Into a round-bottom flask equipped with a stir bar, a reflux condenser and nitrogen on demand were placed phenol **10** (0.14 g, 0.51 mmol), 2'-chloroacetanilide (0.10 g, 0.59 mmol), K_2CO_3 (0.50 g, 3.62 mmol) and acetone (10 mL). The mixture was heated to reflux for 16 h, after which time it was allowed to cool to rt and was poured into a

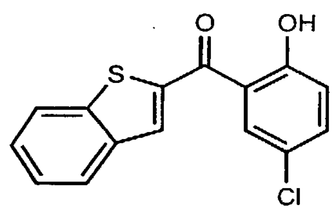
separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to leave orange oil. The product was purified by flash chromatography using 4:1 hexane/ethyl acetate as eluant to provide **9** as a white solid (0.12 g, 58%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.33 (s, 1H), 7.75 (m, 5H), 7.61 (m, 3H), 7.39 (m, 3H), 7.15 (m, 2H), 4.77 (s, 2H).

Example 5



11

Step A:



12

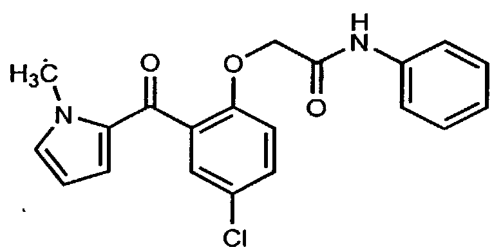
2-Benzothiophenecarboxylic acid (2.51 g, 14.08 mmol), CH_2Cl_2 (35 mL), DMF (4 drops), and oxalyl chloride (1.3 mL, 1.89 g, 14.9 mmol) were used to prepare the corresponding acid chloride according to general procedure V. The acid chloride was used immediately in combination with 4-chloroanisole (2.08 g, 14.59 mmol), $AlCl_3$ (3.15 g, 23.62 mmol) and CH_2Cl_2 (35 mL) according to general procedure I. Compound **12** was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide a yellow solid (2.25 g, 55%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.45 (s, 1H), 8.02 (m, 3H), 7.55 (m, 4H), 7.10 (d, J= 9 Hz, 1H).

Step B:

Into a round-bottom flask equipped with a stir bar, a reflux condenser and nitrogen on demand were placed phenol **12** (0.22 g, 1.23 mmol), 2'-chloroacetanilide (0.22 g, 1.30 mmol), K_2CO_3 (1.46 g, 10.6 mmol) and acetone (25 mL). The mixture was heated to

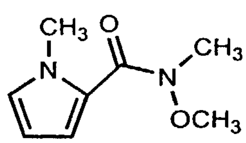
reflux for 16 h, after which time it was allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to leave orange oil. The product was purified by flash chromatography using 4:1 hexane/ethyl acetate as eluant to afford a white solid (0.27 g, 52%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (s, 1H), 7.90 (t, J= 10 Hz, 2H), 7.82 (s, 1H), 7.64 (m, 2H), 7.53 (m, 2H), 7.42 (t, J= 8 Hz, 1H), 7.30 (t, J = 8 Hz, 2H), 7.10 (t, J= 8 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 4.70 (s, 2H).

Example 6



13

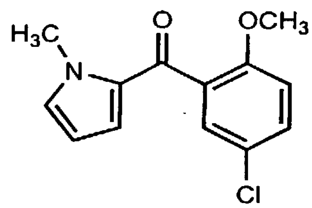
Step A:



14

1-Methyl-2-pyrrolecarboxylic acid (4.75 g, 37.96 mmol), CH_2Cl_2 (100 mL), DMF (0.5 mL) and oxalyl chloride (3.6 mL, 5.24 g, 41.27 mmol) were used according to general procedure V. Into a separate flask were placed N,O-dimethylhydroxylamine hydrochloride (4.45 g, 45.62 mmol), Et_3N (26 mL, 19 g, 187 mmol) and chloroform (100 mL). The resulting solution was cooled to 0 °C and the acid chloride (in 20 mL of chloroform) was added dropwise. The resulting mixture was allowed to stir at 0 °C for an additional 1 h, after which time it was allowed to warm to RT. The mixture was then poured into a separatory funnel containing chloroform and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a brown oil which was used in subsequent reactions with no further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.95 (m, 1H), 6.78 (m, 1H), 6.15 (m, 1H), 3.94 (s, 3H), 3.73 (s, 3H), 3.36 (s, 3H).

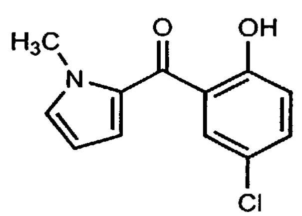
Step B:



15

To a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (5.97 g, 26.95 mmol) and THF (75 mL). The resulting solution was cooled to –78 °C and n-butyl lithium (19.5 mL of a 1.6 M solution in hexane, 31.2 mmol) was added via syringe. The resulting solution was allowed to stir at –78 °C for 30 min and amide **14** (4.2 g, 24.97 mmol in 15 mL THF), was added via syringe. The mixture was allowed to stir at –78 °C for 30 min, after which time it was allowed to warm to RT and stir for an additional 30 min. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a viscous, clear oil which was used in subsequent reactions without any further purification.

Step C:



16

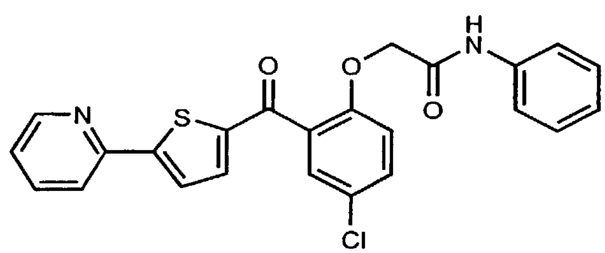
To a round-bottom flask equipped with a stir bar and nitrogen on demand were placed **15** (2.19 g, 8.77 mmol) and CH_2Cl_2 (80 mL). The solution was cooled to –78 °C and boron tribromide (43 mL of a 1.0 M solution in CH_2Cl_2, 43 mmol) was added via syringe. The resulting dark red mixture was allowed to warm to rt and stir for 2 h. The mixture was then carefully poured over ice water, giving a two-phase mixture, which was allowed to stir for 30 min. It was then poured into a separatory funnel containing water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a yellow solid (1.56 g, 75%) which was used in subsequent reactions without any further purification. ^1H NMR ($CDCl_3$,

300 MHz) δ 11.65 (s, 1H), 7.90 (d, J= 3 Hz, 1H), 7.43 (dd, J= 9, 3 Hz, 1H), 7.02 (m, 2H), 6.91 (m, 1H), 6.28 (m, 1H), 4.01 (s, 3H).

Step D:

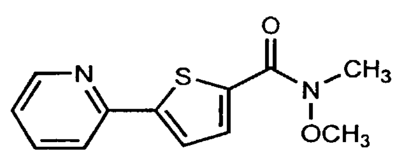
Into a round-bottom flask equipped with a stir bar, a reflux condenser and nitrogen on demand were placed phenol **16** (0.15 g, 0.64 mmol), 2'-chloroacetanilide (0.13 g, 0.78 mmol), K_2CO_3 (0.47 g, 3.39 mmol) and acetone (10 mL). The resulting mixture was heated to reflux for 18 h, after which time it was allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 4:1 hexane/ethyl acetate to afford **13** as a white solid (0.18 g, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.69 (s, 1H), 7.81 (d, J= 9 Hz, 2H), 7.54 (d, J= 3 Hz, 1H), 7.47 (dd, J= 6, 3 Hz, 1H), 7.38 (t, J= 6Hz, 2H), 7.16 (t, J= 6 Hz, 1H), 7.03 (m, 2H), 6.75 (m, 1H), 6.23 (m, 1H), 4.75 (s, 2H), 4.17 (s, 3H).

Example 7



17

Step A:

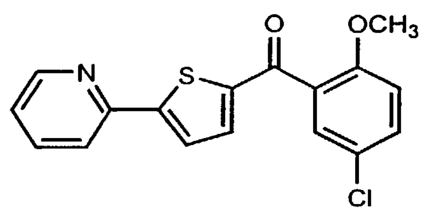


18

5-(2-pyridyl)thiophene-2-carboxylic acid (2.62 g, 12.77 mmol), oxalyl chloride (1.4 mL, 2.04 g, 16.05 mmol), DMF (0.25 mL) and CH_2Cl_2 (25 mL) were used according to general procedure V. The acid chloride was used immediately in the next step without any further purification. Into a separate flask equipped with a stir bar and nitrogen on demand were

placed N,O-dimethylhydroxylamine hydrochloride (1.63 g, 16.71 mmol), Et_3N (9 mL, 6.53 g, 64.57 mmol) and CH_2Cl_2 (25 mL). The resulting solution was cooled to 0 °C, and the acid chloride (in 10 mL of CH_2Cl_2) was added dropwise. When the addition was complete, the mixture was allowed to stir at 0 °C for an additional 30 min, and then was allowed to warm to rt and stir for an additional 1h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure leaving a white solid (2.69 g, 85%). The product was used in subsequent steps without any further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.64 (d, J = 3 Hz, 1H), 8.00 (d, J= 3 Hz, 1H), 7.75 (m, 2H), 7.60 (d, J= 6 Hz, 1H), 7.26 (m, 1H), 3.88 (s, 3H), 3.43 (s, 3H).

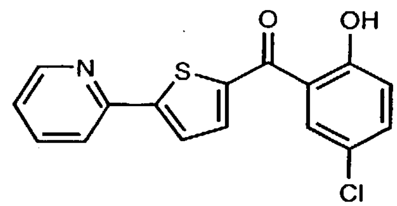
Step B:



19

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (2.42 g, 10.93 mmol) and THF (35 mL). The solution was cooled to –78 °C and n-butyl lithium (7.5 mL of a 1.6 M solution in hexane, 12 mmol) was added via syringe. The resulting yellowish mixture was allowed to stir at – 78 °C for 30 min, after which time amide **18** (2.25 g, 9.06 mmol) in THF (10 mL) was added slowly. The resulting mixture was allowed to stir at –78 °C for 30 min and it was then allowed to warm to rt and stir for an additional 1 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was further purified by flash chromatography using 7:3 hexane/ethyl acetate to afford a yellow solid (1.42 g, 48%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.66 (d, J= 6 Hz, 1H), 7.79 (m, 2H), 7.64 (d, J= 6 Hz, 1H), 7.56 (d, J= 6 Hz, 1H), 7.45 (m ,2H), 7.30 (m, 2H), 6.18 (d, J= 6 Hz, 1H), 3.84 (s, 3H).

Step C:

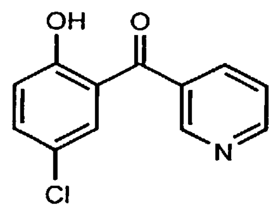


20

Into a round-bottom flask equipped with a stir bar, and nitrogen on demand were placed ketone **19** (1.42 g, 4.31 mmol) and CH_2Cl_2 (70 mL). The mixture was cooled to –78 °C and boron tribromide (20 mL of a 1.0 M solution in CH_2Cl_2, 20 mmol) was added via syringe. The resulting dark red mixture was allowed to stir at –78 °C for 1 h and it was then allowed to warm to rt and stir for an additional 1 h. The mixture was carefully poured over ice water and the resulting two-phase mixture was allowed to stir for 30 min. It was then poured into a separatory funnel containing CH_2Cl_2 and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a tan solid (1.32 g, 97%). ^1H NMR ($CDCl_3$, 300 MHz) δ 11.55 (s, 1H), 8.70 (d, J= 6 Hz, 1H), 8.00 (d, J= 3 Hz, 1H), 7.82 (m, 3H), 7.75 (d, J= 3Hz, 1H), 7.51 (dd, J= 9, 3 Hz, 1H), 7.34 (m, 1H), 7.08 (d, J= 9 Hz, 1H).

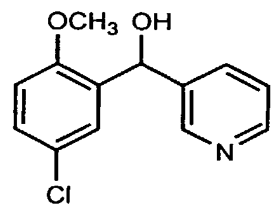
Step D:

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed phenol **20** (0.13 g, 0.42 mmol), 2'-chloroacetanilide (0.10 g, 0.57 mmol), K_2CO_3 (0.29 g, 2.09 mmol) and acetone (10 mL). The resulting mixture was heated to reflux for 18 h, after which time it was allowed to cool to RT and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 65:35 hexane/ethyl acetate as eluant to afford **17** as a white solid (0.16 g, 85%). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.34 (s, 1H), 8.70 (d, J= 6 Hz, 1H), 7.80 (m, 3H), 7.68 (m, 3H), 7.55 (dd, J= 9, 3 Hz, 1H), 7.35 (m, 4H), 7.14 (t, J= 6 Hz, 1H), 7.07 (d, J= 9 Hz, 1H), 4.75 (s, 2H).



21

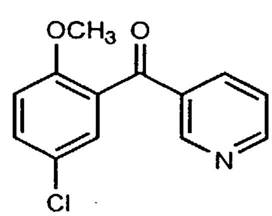
Step A:



22

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (7.02 g, 31.69 mmol) and diethyl ether (Et_2O, 75 mL). The resulting solution was cooled to –78 °C and n-butyl lithium (21 mL of a 1.6 M solution in hexane, 33.6 mmol) was added via syringe. The resulting mixture was allowed to stir at –78 °C for 15 min, after which time 3-pyridinecarboxaldehyde (3.73 g, 34.82 mmol) was added slowly. The resulting solution was allowed to stir at –78 °C for 30 min after which time it was allowed to warm to RT and stir for an additional 30 min. The mixture was poured into a separatory funnel containing Et_2O and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a clear, viscous oil (6.97 g, 88%) which was used without any further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.65 (s, 1H), 8.53 (d, J= 3Hz, 1H), 7.80 (d, J= 9 Hz, 1H), 7.40 (d, J= 3 Hz, 1H), 7.31 (m, 3H), 6.84 (d, J = 9 Hz, 1H), 6.10 (s, 1H), 3.82 (s, 3H).

Step B:



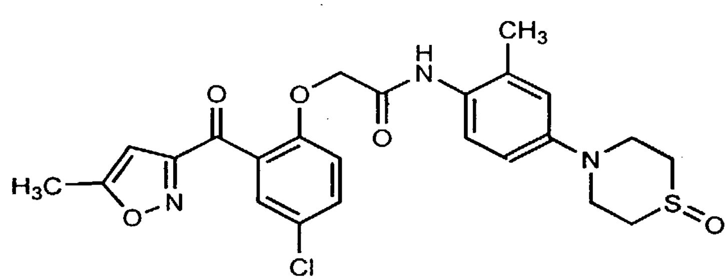
23

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed alcohol **22** (6.97 g, 28 mmol), manganese dioxide (MnO_2, 20.27 g, 233 mmol) and $CHCl_3$ (200 mL). The resulting suspension was heated to reflux for 1 h, after which time it was allowed to cool to rt. The suspension was then filtered through a pad of celite, which was washed with several portions of CH_2Cl_2. The solvents were removed under reduced pressure to afford a tan solid (6.55 g, 95%). The solid was used in subsequent reactions without any further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.94 (d, J= 3 Hz, 1H), 8.81 (dd, J= 6, 3 Hz, 1H), 8.19 (m, 1H), 7.49 (m, 2H), 6.98 (d, J= 9 Hz, 1H), 3.74 (s, 3H).

Step C:

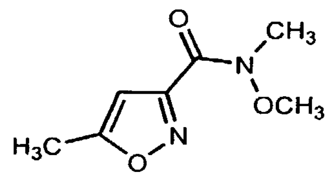
Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed ketone **23** (6.55 g, 26.45 mmol) and CH_2Cl_2 (200 mL). The resulting solution was cooled to –78 °C and boron tribromide (50 mL of a 1.0 M solution in CH_2Cl_2, 50 mmol) was added via syringe. The resulting solution was allowed to stir at –78 °C for 1 h, after which time it was allowed to warm to rt and stir for an additional 30 min. The mixture was carefully poured over ice water and the resulting two-phase system was stirred for 30 min. It was then poured into a separatory funnel containing water and CH_2Cl_2. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **21** as a yellow solid (5.25 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.77 (s, 1H), = 3 Hz, 1H), 8.90 (dd, J = 3, 1.5 Hz, 1H), 8.07 (m, 1H), 7.55 (m, 3H), 7.11 (m, 1H).

Example 9:



24

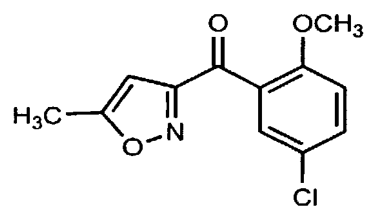
Step A:



25

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed N,O-dimethylhydroxylamine hydrochloride (7.79 g, 79.86 mmol), Et_3N (24 mL, 172.2 mmol) and $CHCl_3$ (150 mL). The resulting solution was cooled to 0 °C and 5-Methyl-3-isoxazolecarbonyl chloride (10.0 g, 68.70 mmol) in $CHCl_3$ (15 mL) was added dropwise, after which the resulting solution was allowed to stir at 0 °C for 1h. The mixture was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a clear oil (10.53 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.92 (s, 1H), 3.75 (br s, 6 H), 2.44 (s, 3H).

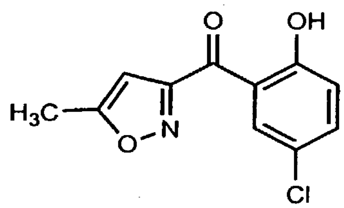
Step B:



26

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (5.02 g, 22.66 mmol) and Et_2O (150 mL). The solution was cooled to −78 °C and n-butyl lithium (15.6 mL of a 1.6 M solution in hexane, 24.96 mmol) was added via syringe. The resulting solution was allowed to stir at −78 °C for 15 min and then amide 25 (4.03 g, 23.68 mmol) in Et_2O (20 mL) was added slowly, after which time the solution was allowed to stir at −78 °C for 30 min. It was then allowed to warm to rt and stir for an additional 2 h. The mixture was then poured over ice water and the two-phase system was stirred for 30 min. It was then poured into a separatory funnel containing Et_2O and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to provide a white solid (5.37 g, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, J= 3 Hz, 1H), 7.42 (dd J= 6, 3 Hz, 1H), 6.92 (d, J = 6 Hz, 1H), 6.45 (s, 1H), 3.76 (s, 3H), 2.49 (s, 3H).

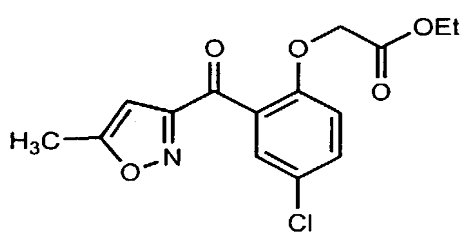
Step C:



27

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed ketone **26** (5.36 g, 21.30 mmol) and CH_2Cl_2 (100 mL). The solution was cooled to –78 °C and boron tribromide (40 mL of a 1.0 M solution in CH_2Cl_2) was added via syringe. The resulting dark red solution was allowed to stir at –78 °C for 1 h, after which time it was allowed to warm to RT and stir for an additional 2 h. The mixture was then carefully poured over ice water and the resulting two-phase system was stirred for 30 min. The mixture was then poured into a separatory funnel containing Et_2O and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a tan solid (5.44 g) which was used in subsequent reactions without any further purification.

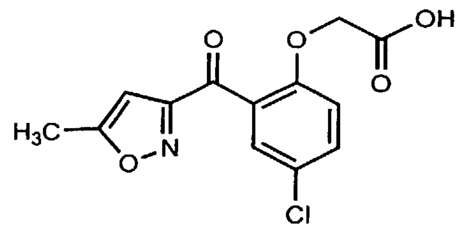
Step D:



28

Phenol **27** (5.44 g crude weight, 21 mmol), ethyl bromoacetate (2.3 mL, 20.74 mmol), K_2CO_3 (12.32 g, 89.14 mmol) and acetone (150 mL) were used according to general procedure II. The product was used in subsequent reactions without any further purification.

Step E:



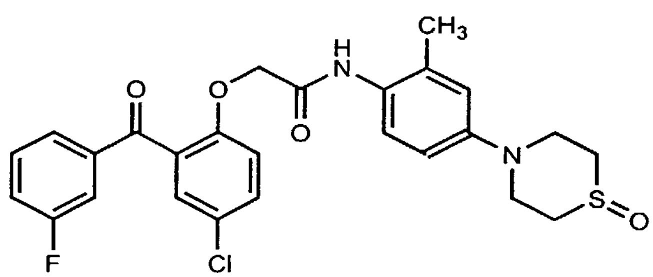
29

Ester **28** (21 mmol), THF (35 mL), EtOH (15 mL), water (15 mL) and LiOH (2.04 g, 48.62 mmol) were used according to general procedure III. Trituration with hexane provided **29** as a white foam, which was used in subsequent reactions without any further purification.

Step F:

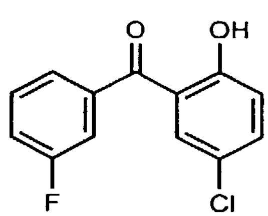
Acid **29** (0.215 g, 0.727 mmol), HOBt (0.112 g, 0.829 mmol), EDAC (0.198 g, 1.03 mmol), Et_3N (0.25 mL, 1.79 mmol), DMF (5 mL) and sulfoxide **399** (0.198 g, 0.884 mmol) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to afford **24** as a tan solid (0.124 g, 34%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.78 (s, 1H), 7.77 (d, J= 4 Hz, 1H), 7.53-7.47 (m, 2H), 6.97 (d, J= 8 Hz, 1H), 6.80 (m, 2H), 6.49 (s, 1H), 4.69 (s, 2H), 3.98-3.92 (m, 2H), 3.53 (m, 2H), 2.94-2.84 (m, 4H), 2.18 (s, 3H), 1.55 (s, 3H).

Example 10:



30

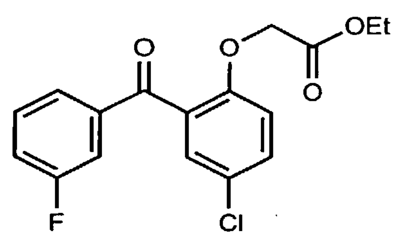
Step A:



31

4-Chloroanisole (4.06 g, 28.47 mmol), 3-fluorobenzoyl chloride (4.53 g, 28.57 mmol), $AlCl_3$ (6.23 g, 46.72 mmol) and CH_2Cl_2 (100 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide the **31** as a yellow solid (2.60 g, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.80 (s, 1H), 7.50 (m, 6H), 7.09 (d, J= 9 Hz, 1H).

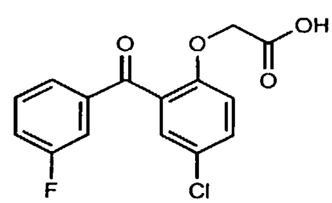
Step B:



32

Phenol **31** (2.60 g, 10.37 mmol), ethyl bromoacetate (1.3 mL, 11.72 mmol), K_2CO_3 (7.15 g, 51.73 mmol), and acetone (80 mL) were used according to general procedure II. The product was used in subsequent reactions without any further purification.

Step C:



33

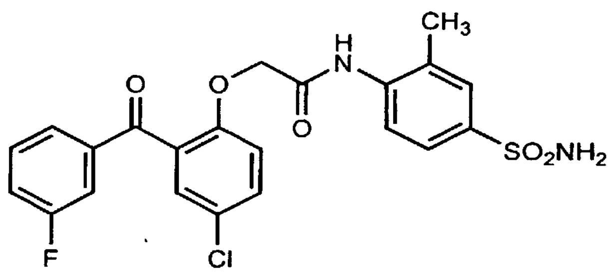
Ester **32** (10 mmol), THF (30mL), EtOH (10 mL), water (10 mL) and LiOH (1.02 g, 24.31 mmol) were used according to general procedure III to afford **33** as a white solid (3.01 g, 98%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.71-7.38 (m, 6H), 6.91 (d, J= 9 Hz, 1H), 4.26 (s, 2H).

Step D:

Acid **33** (0.22 g, 0.71 mmol), HOBt (0.115 g, 0.851 mmol), EDAC (0.205 g, 1.07 mmol) Et_3N (0.25 mL, 1.79 mmol), DMF (5 mL) and sulfoxide **399** (0.185 g, 0.826 mmol) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **30** as a white solid (0.05

g, 14%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (s, 1H), 7.58-7.38 (m, 6H), 7.28 (m, 1H), 7.01 (d, J= 8 Hz, 1H), 6.76 (m, 2H), 4.66 (s, 2H), 3.98-3.91 (m, 2H), 3.53 (m, 2H), 2.91-2.83 (m, 4H), 1.54 (s, 3H).

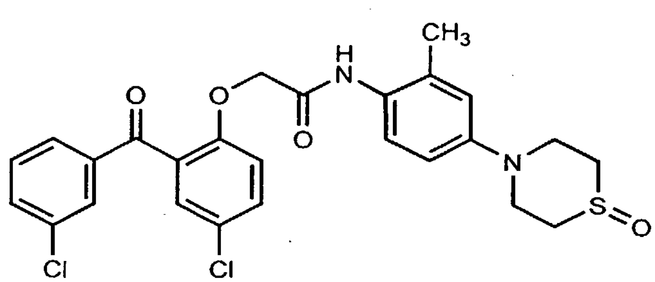
Example 11:



34

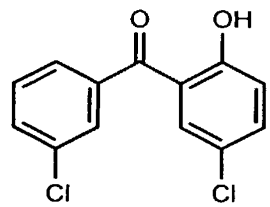
Carboxylic acid **33** (0.224 g, 0.726 mmol), oxalyl chloride (0.2 mL, 2.29 mmol), and CH_2Cl_2 (4 mL) were used according to general procedure V. Into a separate flask were placed sulfonamide **466** (0.158 g, 0.848 mmol), Et_3N (0.25 mL, 1.79 mmol) and acetonitrile (CH_3CN, 8 mL). The mixture was cooled to 0 °C and the acid chloride (in 2 mL CH_3CN) was added dropwise over several minutes. The resulting mixture was allowed to stir at 0 °C for 30 min, after which time it was allowed to warm to RT and stir for an additional 5 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **34** as a white solid (0.117 g, 34%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.39 (s, 1H), 7.71-7.52 (m, 9H), 7.31-7.27 (m, 3H), 4.85 (s, 2H), 2.21 (s, 3H).

Example 12:



35

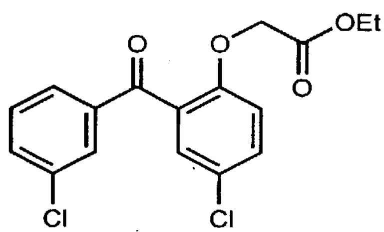
Step A:



36

4-Chloroanisole (4.02 g, 28.19 mmol), 3-chlorobenzoyl chloride (3.8 mL, 4.94 g, 28.22 mmol), $AlCl_3$ (5.62 g, 42.15 mmol) and CH_2Cl_2 (75 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide **36** as a yellow solid (5.35 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (s, 1H), 7.64 (s, 1H), 7.58 (d, J= 8 Hz, 1H), 7.53-7.44 (m, 4H), 7.03 (d, J= 12 Hz, 1H).

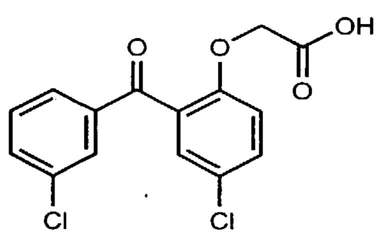
Step B:



37

Phenol **36** (5.35 g, 20.03 mmol), ethyl bromoacetate (2.5 mL, 22.54 mmol), K_2CO_3 (12.91 g, 93.41 mmol), and acetone (125 mL) were used according to general procedure II. The product was used in subsequent reactions without any further purification.

Step C:



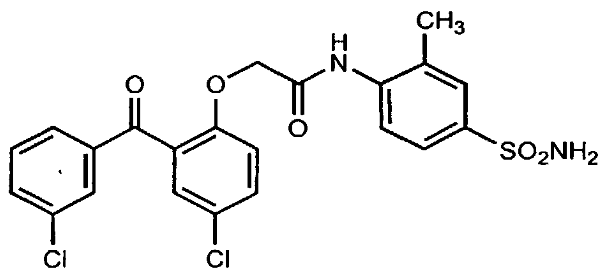
38

Ester **37** (20 mmol), THF (60 mL), EtOH (15 mL), water (15 ml) and LiOH (2.09 g, 49.81 mmol) were used according to general procedure III. The product was used in subsequent reactions without any further purification.

Step D:

Carboxylic acid **38** (0.29 g, 0.892 mmol), sulfoxide **399** (0.24 g, 1.07 mmol), EDAC (0.261 g, 1.36 mmol), HOBt (0.142 g, 1.05 mmol) and DMF (7 mL) were used according to general procedure IV, with the exception that no Et_3N was used. The product was purified by flash chromatography using 97:3 CH_2Cl_2/CH_3OH as eluant to provide **35** as a tan solid (0.34 g, 72%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.21 (s, 1H), 7.86 (d, J= 3 Hz, 1H), 7.72 (d, J = 6Hz, 1H), 7.60-7.43 (m, 4H), 7.07 (d, J = 9 Hz, 2H), 6.85-6.82 (m, 3H), 4.72 (s, 2H), 4.06-3.98 (m, 2H), 3.62 -3.55 (m, 2H), 3.00-2.90 (m, 4H), 2.18 (s 3H).

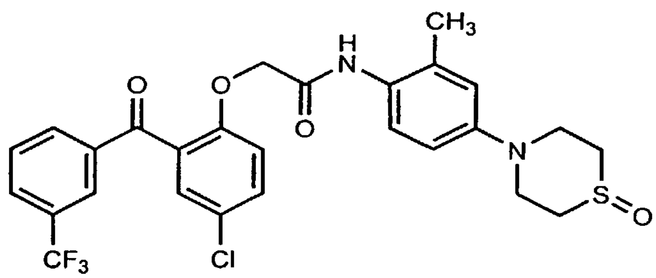
Example 13:



39

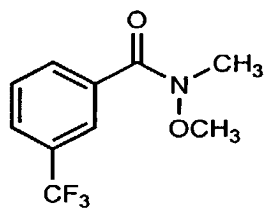
Carboxylic acid **38** (0.229 g, 0.704 mmol), oxalyl chloride (0.2 mL, 2.29 mmol) and CH_2Cl_2 (4 mL) were used according to general procedure V. Into a separate flask were placed sulfonamide **466** (0.156 g, 0.838 mmol), Et_3N (0.25 mL, 1.79 mmol) and CH_3CN (8 mL). The acid chloride (in 2 mL of CH_3CN) was added dropwise over several minutes. The resulting solution was allowed to stir at 0 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 5 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **39** as a white solid (0.110 g, 32%). ^1H NMR (DMSO-d_6, 300 MHz) δ 9.39 (s, 1H), 7.82-7.53 (m, 9H), 7.30 (m, 3H), 4.84 (s, 2H), 2.20 (s, 3H).

Example 14:



40

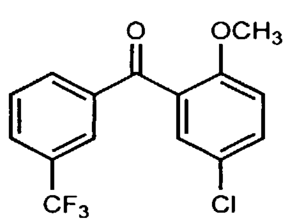
Step A:



41

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed N,O-dimethylhydroxylamine hydrochloride (3.16 g, 32.40 mmol), Et_3N (9 mL, 64.57 mmol) and $CHCl_3$ (85 mL). The solution was cooled to 0 °C and 3-trifluoromethylbenzoyl chloride (4 mL, 5.53 g, 26.52 mmol) was added dropwise over several minutes. The resulting solution was allowed to stir at 0 °C for 30 min, after which time it was allowed to warm to RT and stir for an additional 30 min. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to provide a clear oil which was used without any further purification.

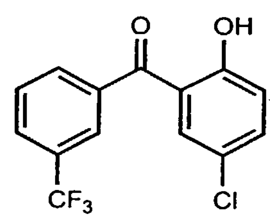
Step B:



42

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (5.23 g, 23.61 mmol) and Et_2O (100 mL). The solution was cooled to –78 °C and n-butyl lithium (17 mL of a 1.6 M solution in hexane, 27.2 mmol) was added dropwise. The resulting mixture was allowed to stir at –78 °C for 15 min, after which time amide **41** (5.56 g, 23.84 mmol) was added dropwise. The mixture was allowed to stir at – 78 °C for 30 min, after which time it was allowed to warm to RT and stir for an additional 2 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to leave a yellow oil, which was used in subsequent reactions without any further purification

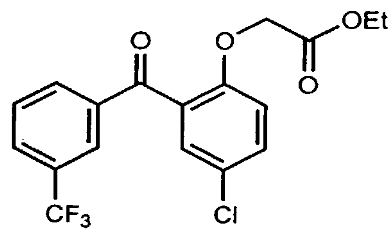
Step C:



43

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed **42** (23 mmol) and CH_2Cl_2 (150 mL). The solution was cooled to –78 °C and boron tribromide (35 mL of a 1.0 M solution in CH_2Cl_2, 35 mmol) was added dropwise over several minutes. The resulting dark mixture was allowed to stir at –78 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 1h. The mixture was carefully poured over ice and the two-phase mixture was stirred for 30 min. It was then poured into a separatory funnel containing CH_2Cl_2 and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a yellow solid (5.04 g, 73%). ^1H NMR ($CDCl_3$, 300 MHz) δ 11.76 (s, 1H), 8.25-7.84 (m, 3H), 7.73 (t, J= 9 Hz, 1H), 7.56-7.52 (m, 2H), 7.12 (d, J= 9 Hz, 1H).

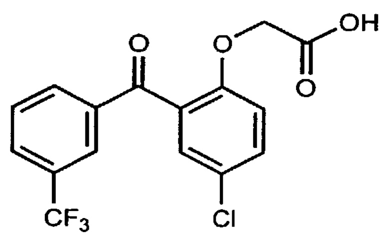
Step D:



44

Phenol **43** (5.04 g, 16.76 mmol), ethyl bromoacetate (2.1 mL, 18.94 mmol), K_2CO_3 (9.01 g, 65.19 mmol) and acetone (100mL) were used according to general procedure II. Removal of the solvents under reduced pressure afforded 44 as an oil (6.28 g, crude weight), which was used in subsequent reactions without any further purification.

Step E:



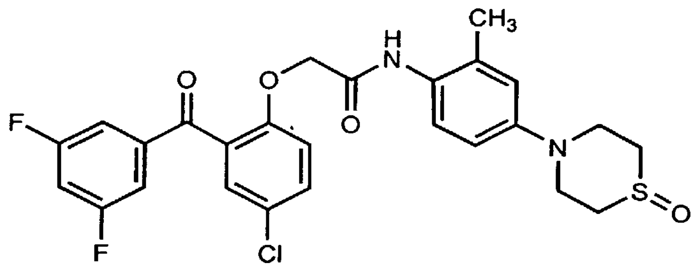
45

Ester **44** (6.28 g, crude weight, 16.24 mmol), THF (50 mL), water (25 mL) and EtOH (25 mL) were used according to general procedure IV. Removal of the solvents under reduced pressure provided acid 45 as a white solid (2.81 g, 48%) which was used without any further purification.

Step F:

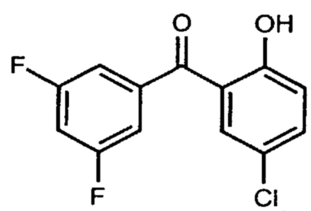
Carboxylic acid **45** (0.208 g, 0.58 mmol), sulfoxide 399 (0.152 g, 0.679 mmol), EDAC (0.19 g, 0.991 mmol), HOBt (0.103 g, 0.76 mmol) and DMF (5 ML) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH to provide 40 as an off-white solid (0.23 g, 70%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, J= 9 Hz, 2H), 8.01 (d, J= 9 Hz, 1H), 7.88 (d, J= 9 Hz, 1H), 7.66 (t, J= 6 Hz, 1H), 7.60 (dd, J= 9, 3 Hz, 1H), 7.50 (d, J= 9 Hz, 1H), 7.44 (d, J= 3 Hz, 1H), 7.09 (d, J= 9 Hz, 1H), 6.83 (m, 3H), 4.72 (s, 2H), 4.05-3.96 (m, 2H), 3.62-3.54 (m, 2H), 3.0-2.89 (m, 4H), 2.16 (s, 3H).

Example 15:



46

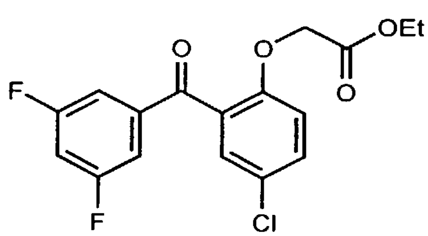
Step A:



47

4-Chloroanisole (4.12 g, 28.89 mmol), 3,5-difluorobenzoyl chloride (5.0 g, 28.3 mmol), $AlCl_3$ (5.65 g, 42.37 mmol) and CH_2Cl_2 (75 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide a yellow solid (2.72 g, 36%). ^1H NMR ($CDCl_3$, 300 MHz) δ 11.64 (s, 1H), 7.54 (m, 2H), 7.23 (m, 2H), 7.11 (m, 2H).

Step B:

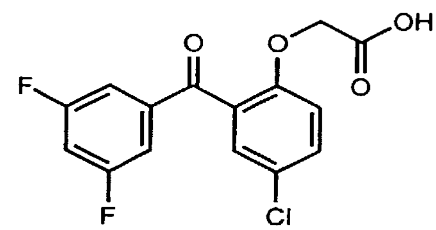


48

Phenol **47** (2.72 g, 10. 13 mmol), ethyl bromoacetate (1.3 mL, 11.7 mmol), K_2CO_3 (5.28 g, 38.2 mmol) and acetone (100 mL) were used according to general procedure II. Removal

of the solvents under reduced pressure afforded 48 as a clear oil (3.8 g, crude weight) that was used without any further purification.

Step C:



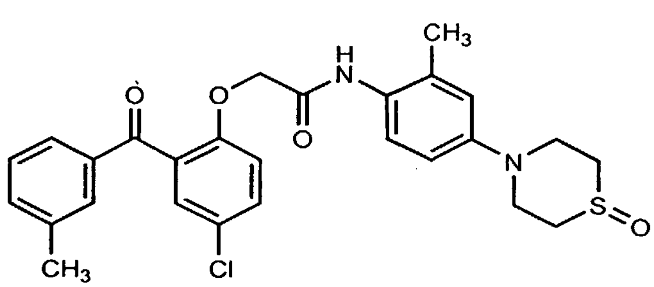
49

Ester **48** (10 mmol), THF (50 mL), water (25 mL) and EtOH (25 mL) were used according to general procedure III. Removal of the solvents under reduced pressure afforded 49 as a white solid, which was used in subsequent reactions without any further purification.

Step D:

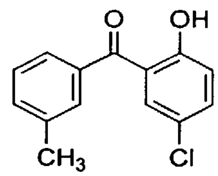
Carboxylic acid **49** (0.20 g, 0.612 mmol), sulfoxide 399 (0.167 g, 1.22 mmol), EDAC (0.23 g, 1.2 mmol), HOBt (0.106 g, 0.784 mmol) and DMF (5 mL) were used according to general procedure IV, with the exception that no Et_3N was used. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant, followed by trituration with Et_2O, afforded **46** as an off-white solid (0.24 g, 74%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 7.61-7.54 (m, 2H), 7.42 (d, J= 3 Hz, 1H), 7.38 (m, 1H), 7.08 (m, 2H), 6.85 (m, 2H), 4.73 (s, 2H), 4.73 (, 2H), 4.05-3.96 (m, 2H), 3.62-3.55 (m, 2H), 2.94-2.89 (m, 4H), 2.21 (s, 3H).

Example 16



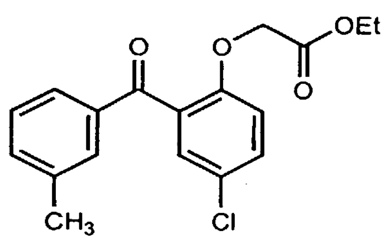
50

Step A:



4-Chloroanisole (4.16 g, 29. 17 mmol), 3-methylbenzoyl chloride (4.42 g, 28.59 mmol), $AlCl_3$ (6.12 g, 45.9 mmol) and CH_2Cl_2 (150 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/CH_2Cl_2 as eluant to provide **50** as yellow solid (1.54 g, 22%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.91 (s, 1H), 7.54 (d, J= 4 Hz, 1H), 7.47-7.39 (m, 5H), 7.02 (d, J= 8 Hz, 1H), 2.44 (s, 3H).

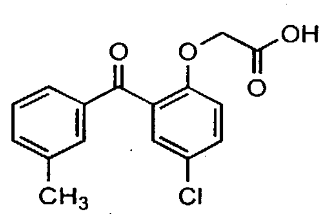
Step B:



51

Phenol **50** (1.54 g, 6.24 mmol), ethyl bromoacetate (0.8 mL, 7.21 mmol), K_2CO_3 (3.15 g, 22.79 mmol) and acetone (35 mL) were used according to general procedure II. Removal of the solvents under reduced pressure afforded 51 as a clear oil that was used without any further purification.

Step C:



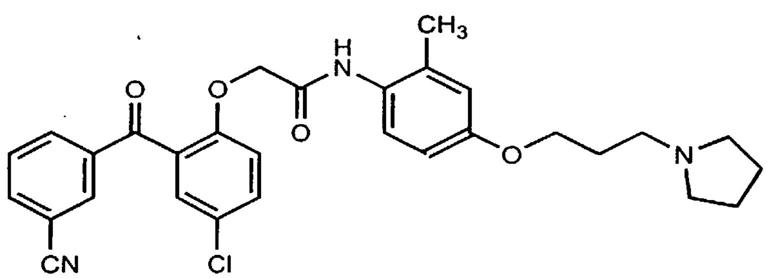
52

Ester **51** (6.3 mmol), lithium hydroxide (0.700 g, 16.68 mmol), THF (20 mL), water (10 mL) and EtOH (10 mL) were used according to general procedure III. Removal of the solvents under reduced pressure afforded **52** as a white solid (1.82 g, 96%) which was used without any further purification.

Step D:

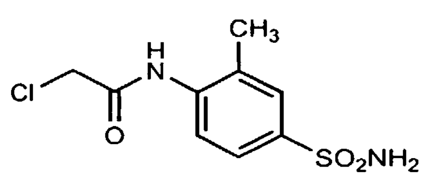
Carboxylic acid **52** (0.21 g, 0.70 mmol), sulfoxide 399 (0.19 g, 0.853 mmol), EDAC (0.212 g, 1.11 mmol), HOBt (0.121 g, 0.895 mmol) and DMF (5 mL) were used according to general procedure IV, with the exception that no Et_3N was used. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **50** as an off-white solid (0.09 g, 25%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 (s, 1H), 7.69-7.30 (m, 8H), 7.04 (d, J= 9 Hz, 1H), 6.81 (m, 3H), 4.69 (s, 2H), 4.05-3.96 (m, 2H), 3.60-3.51 (m, 2H), 2.93-2.85 (m, 4H), 2.38 (s, 3H), 2.14 (s, 3H).

__Example 17__



53

Carboxylic acid **129** (0.316 g, 1.00 mmol), amine **143** (0.241 g, 1.03 mmol), EDAC (0.251 g, 1.31 mmol), HOBt (0.167 g, 1.24 mmol) and DMF (5 mL) were used according to general procedure IV, with the exception that no Et_3N was used. The product was purified by flash chromatography using 9:1 $CHCl_3/CH_3OH$ as eluant to provide **53** as a tan powder (0.082 g, 15%).

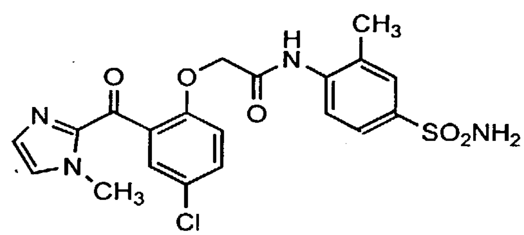


54

Into a round-bottom flask were placed aniline **466** (0.246 g, 1.32 mmol), Et_3N (0.9 mL, 0.65 g, 6.5 mmol), $CHCl_3$ (5 mL) and CH_3CN (5 mL). The resulting mixture was cooled to 0 °C and 2'-chloroacetyl chloride (0.2 mL, 2.51 mmol) was added dropwise over several

minutes. The mixture was allowed to stir at 0 °C for 30 minutes and was then allowed to warm to rt and stir for an additional 30 minutes. The mixture was then poured into a separatory funnel containing H_2O and ethyl acetate. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a dark, green oil. Several portions of hexane were added and subsequently removed under reduced pressure to afford **54** as a green solid, which was used without any further purification. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.84 (s, D 1H), 7.69 (m, 3H), 7.31 (s, 2H), 4.38 (s, 2H), 2.31 (s, 3H).

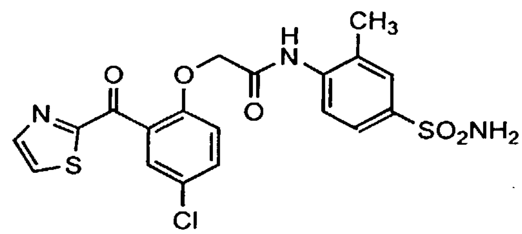
Example 18



55

Into a round-bottom flask were placed amine **54** (0.16 g, 0.61 mmol), phenol 185 (0.14 g, 0.60 mmol), K_2CO_3 (0.66 g, 4.8 mmol) and acetone (10 mL). The resulting mixture was allowed to heat to reflux and stir overnight. The mixture was then allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH to provide **55** as an off-white solid (0.02 g, 7%). ^1H NMR (DMSO-d_6, 400 MHz) δ 9.74 (s, 1H), 7.63-7.53 (m, 4H), 7.26-7.19 (m, 4H), 6.97 (s, 2H), 4.81 (s, 2H), 3.99 (s, 3H), 2.08 (s, 3H).

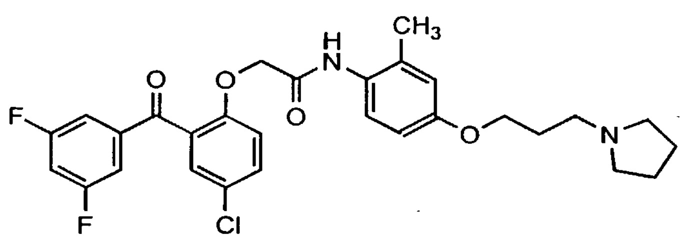
Example 19



56

Into a round-bottom flask were placed amine **54** (0.16 g, 0.62 mmol), K_2CO_3 (0.51 g, 3.7 mmol), phenol **4** (0.22 g, 0.90 mmol) and acetone (5 mL). The same procedure was followed as in example 55. The product was purified by flash chromatography using 97:3 $CHCl_3/CH_3OH$ to provide **56** as a tan solid (0.03 g, 10%). ^1H NMR (DMSO-d_6, 300 MHz) δ 9.39 (s, 1H), 8.33 (d, J= 3 Hz, 1H), 8.16 (d, J= 3 Hz, 1H), 7.83-7.64 (m, 5H), 7.39-7.30 (m, 3H), 4.86 (s, 2H), 2.23 (s, 3H).

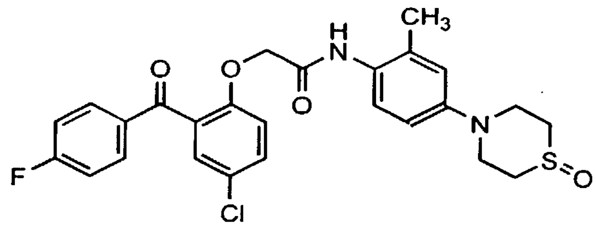
Example 20



57

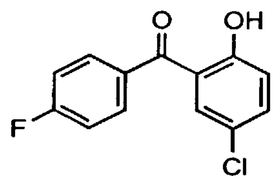
Acid **49** (0.351 g, 1.07 mmol), amine **143** (0.253 g, 1.08 mmol), EDAC (0.341 g, 1.78 mmol), HOBt (0.193 g, 1.43 mmol) and DMF (7 mL) were used according to general procedure IV, with the exception that no Et_3N was used. The product was purified by flash chromatography using 9:1 $CHCl_3/CH_3OH$ to provide a tan solid (0.09 g, 15%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.19 (s, 1H), 7.49 (dd, J= 9, 3 Hz, 1H), 7.42 (d, J= 9 Hz, 1H), 7.33 (d, J = 3 Hz, H), 7.27 (d, J= 3 Hz, 1H), 7.19 (m, 1H), 7.01-6.96 (m, 2H), 6.65-6.63 (m, 2H), 4.62 (s, 2H), 4.00-3.96 (t, J= 6 Hz, 2H), 3.76 (m, 2H), 3.23-3.15 (m, 2h), 2.75 (m, 2H), 2.39-2.12 (m, 6H), 2.09 (s, 3H).

Example 21



58

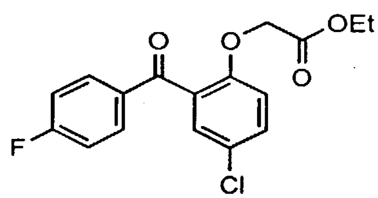
Step A:



59

4-Fluorobenzoyl chloride (3.2 mL, 27.08 mmol), 4-chloroanisole (3.98 g, 27.91 mmol), aluminum chloride (5.78 g, 43.34 mmol) and dichloromethane (120 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/ethyl acetate to provide **59** as a yellow solid (3.48 g, 51%).

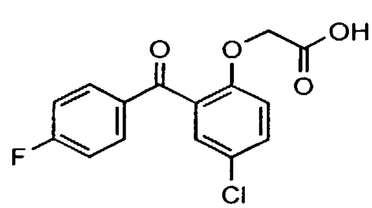
Step B:



60

Phenol **59** (3.48 g, 13.88 mmol), ethyl bromoacetate (1.7 mL, 15.32 mmol), K_2CO_3 (7.74 g, 56.0 mmol) and acetone were used according to general procedure II to provide **60** as a white solid, which was washed with several portions of ether, dried in vacuo and used in subsequent reactions without any further purification.

Step C:



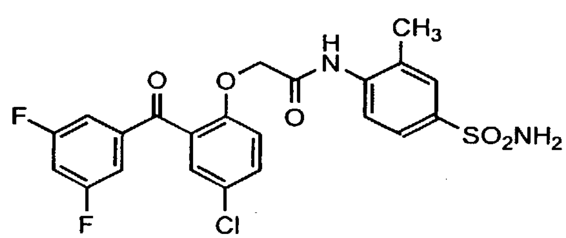
61

Ester **60** (4.7 g, 13.9 mmol), lithium hydroxide (1.45 g, 34.56 mmol), water (20 mL), THF (40 mL) and EtOH (20 mL) were used according to general procedure III to afford **61** as a viscous, clear oil. Ether was added to the oil causing a white solid to form, which was filtered and dried to provide 61 as a white solid, which was used without any further purification.

Step D:

Carboxylic acid **61** (0.237 g, 0.786 mmol), sulfoxide 399 (0.198 g, 0.88 mmol), EDAC (0.285 g, 1.49 mmol), HOBt (0.131 g, 0.97 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **58** as a tan solid (0.280 g, 71%). ^1H NMR (DMSO-d-$_6$, 300 MHz) δ 8.95 (s, 1H), 7.90 (m, 2H), 7.66 (dd, J= 9, 3 Hz, 1H), 7.49 (d, J= 3 Hz, 1H), 7.36 (t, J= 6 Hz, 2H), 7.26 (d, J= 9 Hz, 1H), 7.14 (d, J= 9 Hz, 1H), 6.84 (m, 2H), 4.73 (s, 2H), 3.75 (m, 2H), 3.58 (m, 2H), 2.91 (m, 2H), 2.71 (m, 2H), 2.03 (s, 3H).

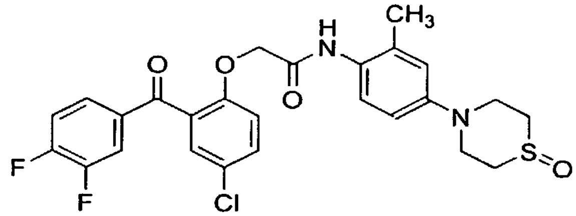
<u>**Example 22**</u>



62

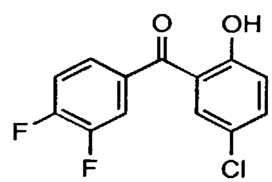
Carboxylic acid **49** (0.123 g, 0.377 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (2 drops) and chloroform (5 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, sulfonamide **466** (0.07 g, 0.37 mmol), $NaHCO_3$ (0.13 g, 1.55 mmol), water (1 mL) and acetone (5 mL) were used according to general procedure VI to afford 62 as a tan solid (0.07 g, 40%). ^1H NMR (DMSO-d$_6$, 300 MHz) δ 9.46 (s, 1H), 7.68-7.45 (m, 8H), 7.28 (m, 3H), 4.85 (s, 2H), 2.21 (s, 3H).

<u>**Example 23**</u>



63

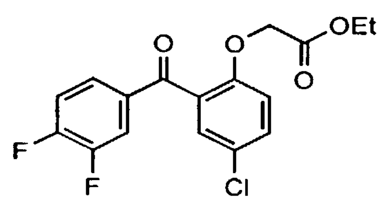
Step A:



64

3,4-Difluorobenzoyl chloride (5.01 g, 28.37 mmol), 4-chloroanisole (4.04 g, 28.33 mmol), aluminum chloride (5.61 g, 42.07 mmol) and dichloromethane (100 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/ethyl acetate as eluant to provide **64** as a yellow solid (2.65 g, 35%). ^1H NMR ($CDCl_3$, 300 MHz) δ 11.64 (s, 1H), 7.64-7.30 (m, 5H), 7.09 (d, J= 9 Hz, 1H).

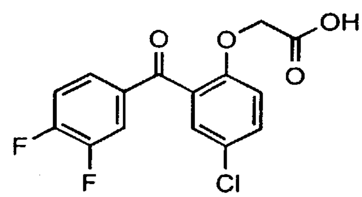
Step B:



65

Phenol **64** (2.65 g, 9.86 mmol), ethyl bromoacetate (1.20 mL, 10.82 mmol), K_2CO_3 (5.37 g, 38.85 mmol) and acetone (35 mL) were used according to general procedure II to provide 65 as white solid (3.39 g, 96%) that was used without any further purification.

Step C:



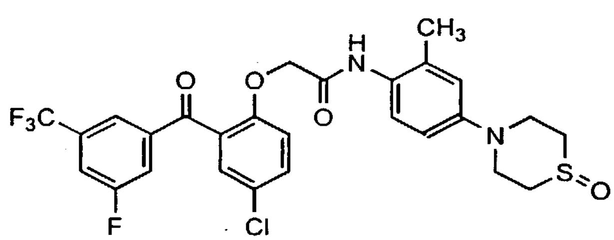
66

Ester **65** (3.39 g, 9.56 mmol), lithium hydroxide (0.80 g, 19.07 mmol), water (20 mL), THF (40 mL) and EtOH (20 mL) were used according to general procedure III to provide **66** as a white solid which was used without any further purification.

Step D:

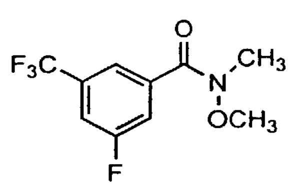
Carboxylic acid **66** (0.146 g, 0.447 mmol), sulfoxide **399** (0.096 g, 0.429 mmol), EDAC (0.183 g, 0.955 mmol), HOBt (0.077 g, 0.569 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **63** as a tan solid (0.150 g, 63%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.35 (s, 1H), 7.79-7.56 (m, 3H), 7.41 (d, J= 3 Hz, 1H), 7.32 (m, 2H), 7.09 (d, J= 9 Hz, 1H), 6.87 (br s, 1H), 4.73 (s, 2H), 4.04 (m, 2H), 3.58 (m, 2H), 3.02 (m, 4H), 1.62 (s, 3H).

__Example 24__



67

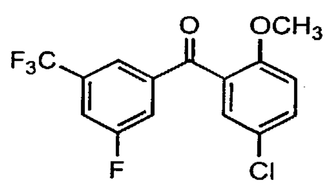
Step A:



68

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed N,O-dimethylhydroxylamine hydrochloride (2.80 g, 28.7 mmol), Et_3N (9.0 mL, 64.57 mmol) and $CHCl_3$ (50 mL). The solution was cooled to 0 °C and 3-trifluoromethyl-5-fluorobenzoyl chloride (5.0 g, 22.07 mmol) was added dropwise over several minutes. The resulting solution was allowed to stir at 0 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 30 min. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to provide **68** as a clear oil which was used without any further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 (s, 1H), 7.65 (d, J= 9 Hz, 1H), 7.46 (d, J= 9 Hz, 1H), 3.59 (s, 3H), 3.42 (s, 3H).

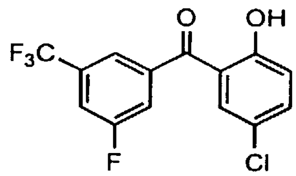
Step B:



69

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-bromo-4-chloroanisole (4.05 g, 18.29 mmol) and Et_2O (75 mL). The solution was cooled to –78 °C and n-butyl lithium (13 mL of a 1.6 M solution in hexane, 20.8 mmol) was added dropwise. The resulting mixture was allowed to stir at –78 °C for 15 min, after which time amide **68** (5.04 g, 20.07 mmol) was added dropwise. The mixture was allowed to stir at – 78 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 2 h. The mixture was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure afford 69 as a yellow solid (6.14 g, 92%), which was used in subsequent reactions without any further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84 (s, 1H), 7.68 (d, J= 9 Hz, 1H), 7.58-7.51 (m, 2H), 7.44 (d, J= 3 Hz, 1H), 7.00 (d, J= 9 Hz, 1H), 3.74 (s, 3H).

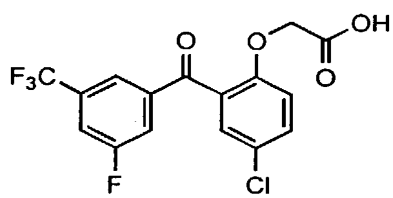
Step C:



70

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed **69** (6.14 g, 18.46 mmol) and CH_2Cl_2 (100 mL). The solution was cooled to –78 °C and boron tribromide (50 mL of a 1.0 M solution in CH_2Cl_2, 50 mmol) was added dropwise over several minutes. The resulting dark mixture was allowed to stir at –78 °C for 30 min, after which time it was allowed to warm to rt and stir for an additional 1h. The mixture was carefully poured over ice and the two-phase mixture was stirred for 30 min. It was then poured into a separatory funnel containing CH_2Cl_2 and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **70** as a yellow solid (5.68 g, 96%), which was used without any further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 11.61 (s, 1H), 7.77 (s, 1H), 7.65-7.54 (m, 3H), 7.47 (d, J= 3 Hz, 1H), 7.12 (d, J= 9 Hz, 1H).

Step D:



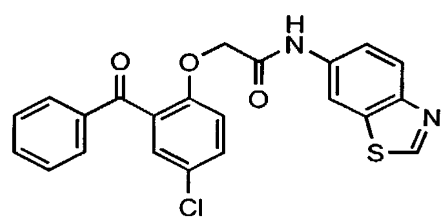
71

Phenol **70** (5.68 g, 17.83 mmol), ethyl bromoacetate (2 mL, 18.03 mmol), K_2CO_3 (9.61 g, 69.53 mmol) and acetone (35 mL) were used according to general procedure II to provide the ester as a yellow, viscous oil which was used without any further purification. The ester (6.83 g, 16.88 mmol), lithium hydroxide (1.42 g, 33.84 mmol), water (20 mL), THF (50 mL) and EtOH (20 mL) were used according to general procedure III. The product was washed with several portions of ether to provide **71** as a white solid that was used without any further purification.

Step E:

Carboxylic acid **71** (0.168 g, 0.445 mmol), sulfoxide **399** (0.098 g, 0.438 mmol), EDAC (0.211 g, 1.10 mmol), HOBt (0.076 g, 0.562 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 CH_2Cl_2/CH_3OH as eluant to provide **67** as a white solid (0.18 g, 69%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.26 (s, 1H), 7.92 (s, 1H), 7.73 (d, J= 6 Hz, 1H), 7.64-7.59 (m, 3H), 7.44 (d, J= 3 Hz, 1H), 7.10 (d, J= 9 Hz, 1H), 6.90 (m, 1H), 4.74 (s, 2H), 4.03 (m, 2H), 3.58 (m, 2H), 3.02 (m, 4H), 2.21 (s, 3H).

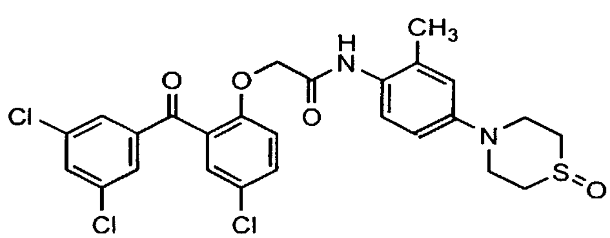
Example 25



72

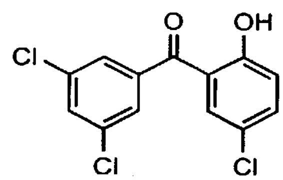
Carboxylic acid **105** (0.195 g, 0.65 mmol), 6-aminobenzthiazole (Lancaster, 0.105 g, 0.70 mmol), EDAC (0.23 g, 1.20 mmol), HOBt (0.105 g, 0.78 mmol) and DMF (5 mL) were used according to general procedure IV, with the exception that no Et_3N was used. The product was purified by flash chromatography using 1:1 hexane/ethyl acetate as eluant to provide **72** as a white solid (0.24 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.51 (s, 1H), 8.92 (s, 1H), 8.64 (s, 1H), 8.08 (d, J= 8 Hz, 1H), 7.92 (d, J= 8 Hz, 1H), 7.67-7.63 (m, 2H), 7.55-7.50 (m, 3H), 7.42 (s, 1H), 7.04 (d, J= 8 Hz, 1H), 4.73 (s, 2H).

Example 26



73

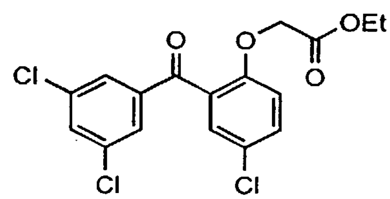
Step A:



74

3,5-Dichlorobenzoyl chloride (5.0 g, 23.87 mmol), 4-chloroanisole (3.40 g, 23.84 mmol), aluminum chloride (5.56 g, 41.70 mmol) and dichloromethane (100 mL) were used according to general procedure I. The product was purified by flash chromatography using 7:3 hexane/dichloromethane to provide **74** as a yellow solid (1.18 g, 16%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.62 (s, 1H), 7.65 (s, 1H), 7.56-7.49 (m, 4H), 7.09 (d, J= 9 Hz, 1H).

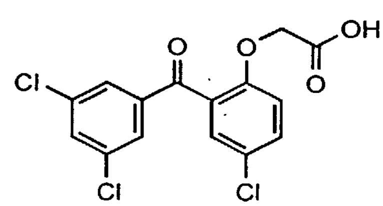
Step B:



75

Phenol **74** (1.18 g, 3.91 mmol), ethyl bromoacetate (0.6 mL, 5.41 mmol), K_2CO_3 (2.66 g, 19.25 mmol) and acetone (15 mL) were used according to general procedure II to afford **75** as a viscous, yellow oil, which was used without any further purification.

Step C:



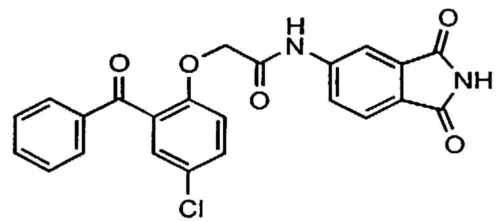
76

Ester **75** (3.9 mmol), lithium hydroxide (0.396 g, 9.44 mmol), water (10 mL), THF (40 mL) and EtOH (10 mL) were used according to general procedure III to afford 76 as a white solid, which was washed with hexane and dried in vacuo (1.32 g, 94%).

Step D:

Carboxylic acid **76** (0.128 g, 0.356 mmol), sulfoxide **399** (0.076 g, 0.339 mmol), EDAC (0.114 g, 0.595 mmol), HOBt (0.057 g, 0.422 mmol) and DMF (5 ML) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 chloroform/methanol as eluant to afford **73** as a white solid (0.125 g, 65%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (s, 1H), 7.70 (s, 1H), 7.62-7.59 (m, 2H), 7.42 (d, J= 3 Hz, 1H), 7.08 (d, J= 9 Hz, 1H), 6.86 (br s, 2H), 4.72 (s, 2H), 4.04 (m, 2H), 3.62-3.55 (m, 2H), 3.06-2.92 (m, 4H), 2.21 (s, 3H).

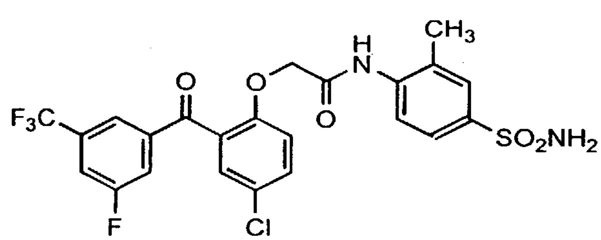
Example 27



77

Carboxylic acid **105** (0.125 g, 0.417 mmol), 3-aminophthalimide (TCI, 0.062 g, 0.382 mmol), EDAC (0.132 g, 0.689 mmol), HOBt (0.063 g, 0.467 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **77** as a white solid (0.038 g, 22%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.10 (s, 1H), 8.39 (s, 1H), 8.25 (dd, J= 9, 3 Hz, 1H), 7.97 (d, J= 9 Hz, 2H), 7.80 (d, J= 9 Hz, 1H), 7.73 (t, J= 6 Hz, 1H), 7.63-7.56 (m, 4H), 7.48 (d, J= 3 Hz, 1H), 7.10 (d, J= 9 Hz, 1H), 4.82 (s, 2H).

Example 28

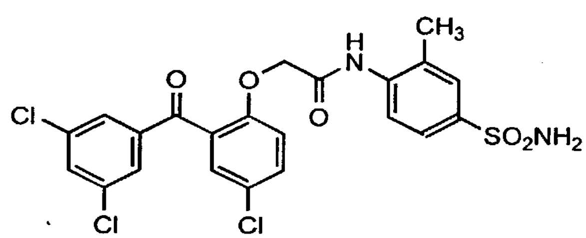


78

Carboxylic acid **71** (11.24 g, 29.84 mmol), oxalyl chloride (3.9 mL, 44.71 mmol), DMF (5 mL) and chloroform (250 mL) were used according to general procedure V to prepare the

acid chloride, which was used without further purification. The acid chloride, sulfonamide **466** (5.12 g, 27.49 mmol), $NaHCO_3$ (11.12 g, 132 mmol), acetone (300 mL) and water (10 mL) were used according to general procedure VI. The product was purified by crystallization from a mixture of acetonitrile/water to provide **78** as a white solid (9.01 g, 60%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.47 (s, 1H), 8.05 (d, J= 9 Hz, 1H), 7.93-7.90 (m, 2H), 7.73-7.50 (m, 5H), 7.30-7.26 (m, 3H), 4.84 (s, 2H), 2.19 (s, 3H). Anal Calcd. for $C_{23}H_{17}ClF_4N_2O_5S$: C, 50.70; H, 3.14; N, 5.14. Found: C, 50.75; H, 3.10; N, 5.21.

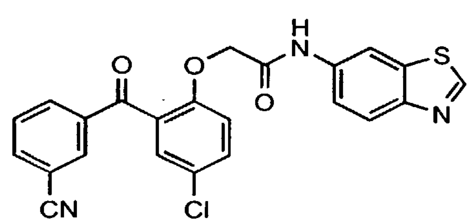
Example 29



79

Carboxylic acid **76** (0.157 g, 0.437 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (3 drops) and dichloromethane (5 mL) were used according to general procedure V to prepare the acid chloride, which was used without any further purification. The acid chloride, sulfonamide **466** (0.072 g, 0.387 mmol), $NaHCO_3$ (0.210 g, 2.5 mmol), acetone (5 mL) and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **79** as a white solid (0.117 g, 57%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.45 (s, 1H), 7.94 (s, 1H), 7.76 (s, 2H), 7.75-7.55 (m, 5H), 7.30-7.25 (m, 3H), 4.85 (s, 2H), 2.22 (s, 3H).

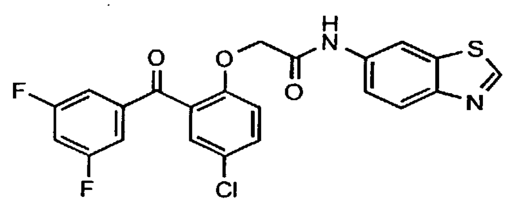
Example 30



80

Carboxylic acid **131** (0.109 g, 0.345 mmol), 6-aminobenzthiazole (Lancaster, 0.056 g, 0.373 mmol), EDAC (0.164 g, 0.855 mmol), HOBt (0.064 g, 0.474 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford 80 as a white solid (0.120 g, 77%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.18 (s, 1H), 9.30 (s, 1H), 8.50 (s, 1H), 8.26 (s, 1H), 8.13 (d, J= 9 Hz, 1H), 8.05 (t, J= 9 Hz, 2H), 7.75-7.66 (m, 2H), 7.56 (m, 2H), 7.26 (d, J= 9 Hz, 1H), 4.81 (s, 2H).

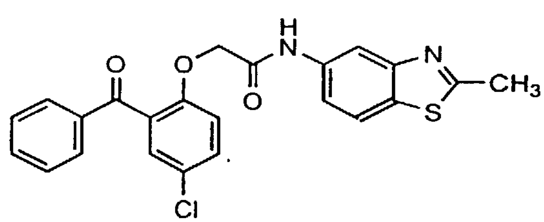
Example 31



81

Carboxylic acid **49** (0.106 g, 0.324 mmol), 6-aminobenzthiazole (Lancaster, 0.051 g, 0.3393 mmol), EDAC (0.158 g, 0.824 mmol), HOBt (0.0584 g, 0.429 mmol) and DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **81** as a white solid (0.105 g, 70%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.22 (s, 1H), 9.31 (s, 1H), 8.48 (d, J= 3 Hz, 1H), 8.04 (d, J= 9 Hz, 1H), 7.67 (dd, J= 9, 3 Hz, 1H), 7.59-7.48 (m, 5H), 7.25 (d, J= 9 Hz, 1H), 4.82 (s, 2H).

Example 32

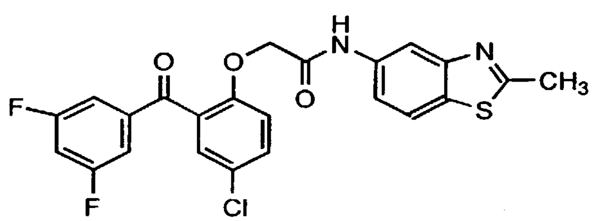


82

Carboxylic acid **105** (0.129 g, 0.43 mmol), oxalyl chloride (0.1 mL, 1.1 5mmol), DMF (4 drops) and dichloromethane (3 mL) were used to prepare the acid chloride according to

general procedure V. The acid chloride, 5-amino-2-methylbenzthiazole dihydrochloride (0.087 g, 0.367 mmol), $NaHCO_3$ (0.324 g, 3.86 mmol), water (0.5 mL) and acetone (5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford 82 as a white solid (0.118 g, 74%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.02 (s, 1H), 8.20 (d, J= 3 Hz, 1H), 7.95 (d, J= 9 Hz, 1H), 7.85 (d, J= 9 Hz, 2H), 7.66-7.47 (m, 6H), 7.26 (d, J= 9 Hz, 1H), 4.78 (s, 2H), 2.80 (s, 3H).

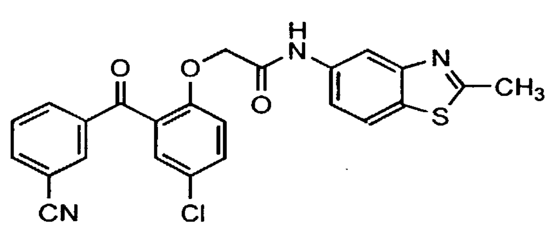
Example 33



83

Carboxylic acid **49** (0.110 g, 0.337 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (5 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, 5-amino-2-methylbenzthiazole dihydrochloride (0.078 g, 0.329 mmol), $NaHCO_3$ (0.293 g, 3.49 mmol), water (0.5 mL) and acetone (5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **83** as a white solid (0.079 g, 49%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.12 (s, 1H), 8.22 (s, 1H), 7.95 (d, J= 9 Hz, 1H), 7.67 (dd, J= 9, 3 Hz, 1H), 7.58-7.48 (m, 5H), 7.25 (d, J= 9 Hz, 1H), 4.81 (s, 2H), 2.80 (s, 3H).

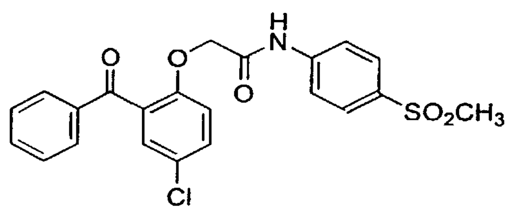
Example 34



84

Carboxylic acid **129** (0.094 g, 0.298 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (5 mL) were used to prepared the acid chloride according to general procedure V. The acid chloride, 5-amino-2-methylbenzthiazole dihydrochloride (0.068 g, 0.287 mmol), $NaHCO_3$ (0.310 g, 3.69 mmol), water (0.5 mL) and acetone (5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 95:5 chloroform/methanol to afford **84** as a tan solid (0.042 g, 31%). ^1H NMR (DMSO-d_6, 300 MHz) δ 10.09 (s, 1H), 8.22 (d, J= 9 Hz, 2H), 8.13 (d, J= 6Hz, 1H), 8.06 (d, J= 9 Hz, 1H), 7.94 (d, J= 9 Hz, 1H), 7.75-7.66 (m, 2H), 7.55 (d, J= 3 Hz, 1H), 7.49 (d, J= 3 Hz, 1H), 7.25 (d, J= 6 Hz, 1H), 4.78 (s, 2H), 2.80 (s, 3H).

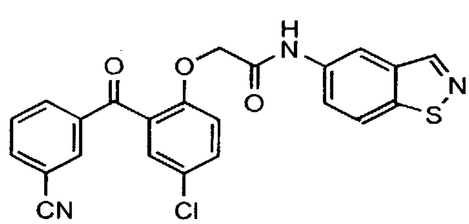
Example 35



85

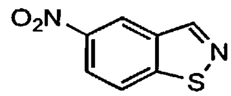
Carboxylic acid **105** (0.104 g, 0.347 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (4 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, 4-methylsulfonlylaniline (0.06 g, 0.350 mmol), $NaHCO_3$ (0.214 g, 2.55 mmol), water (0.5 mL) and acetone (6 mL) were used according to general procedure VI. The product was purified by flash chromatography using 3:2 ethyl acetate/hexane to afford **85** as a white solid (0.061 g, 40%). ^1H NMR (DMSO-d_6, 300 MHz) δ 10.34 (s, 1H), 7.90-7.76 (m, 6H), 7.66-7.47 (m, 5H), 7.22 (d, J= 9 Hz, 1H), 3.18 (s, 3H).

Example 36



86

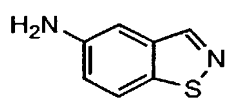
Step A:



87

Into a stirred Parr bomb were placed 2-chloro-5-nitrobenzaldehyde (1.84 g, 9.92 mmol), sulfur (0.360 g, 11.23 mmol), ammonia (5 mL) and methanol (30 mL). The bomb was sealed and was heated, with stirring, to 85-90 °C for 16 h. The mixture was allowed to cool to rt and was poured into a separatory funnel containing dichloromethane and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed to afford **87** as an orange solid (1.26 g, 70%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.33 (s, 1H), 9.13 (d, J= 4 Hz, 1H), 8.47 (d, J= 12 Hz, 1H), 8.36 (dd, J= 12, 4 Hz, 1H).

Step B:



88

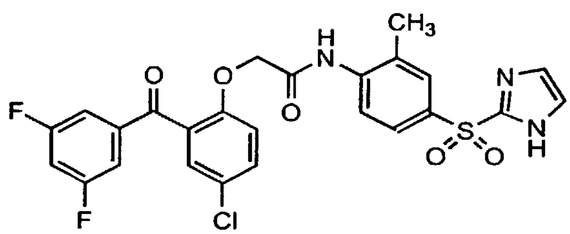
Compound **87** (1.26 g, 6.97 mmol), iron powder (1.89 g, 33.84 mmol), concentrated hydrochloric acid (7 mL) and ethanol (35 mL) were added to a round-bottom flask. The mixture was heated to reflux and stirred for 2 h, after which time it was allowed to cool to rt. The mixture was then poured into water and was made basic by the slow addition of solid $NaHCO_3$. It was then poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **88** as a tan solid (0.470 g, 45%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.82 (s, 1H), 7.81 (d, J= 9 Hz, 1H), 7.20 (d, J= 3 Hz, 1H), 6.99 (dd, J= 9, 3Hz, 1H), 5.40 (s, 2H).

Step C:

Carboxylic acid **129** (0.125 g, 0.396 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and dichloromethane (5 mL) were used to prepare the acid chloride according to

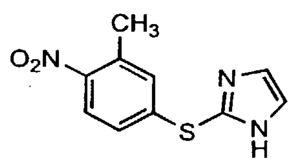
general procedure V. The acid chloride, amine **88** (0.063 g, 0.419 mmol), $NaHCO_3$ (0.173 g, 2.06 mmol), water (0.5 mL) and acetone (5 mL) were used according to general procedure VI to afford a yellow solid. The solid was washed with several portions of ether and was dried in vacuo to provide **86** as a yellow solid (0.083 g, 47%).

Example 37



89

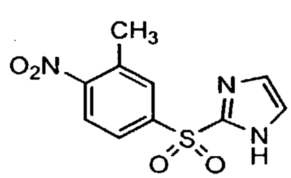
Step A:



90

Into a round-bottom flask were placed 5-fluoro-2-nitrotoluene (Lancaster, 2.03 g, 13.09 mmol), 2-thioimidazole (1.54 g, 15.38 mmol), K_2CO_3 (6.31 g, 45.66 mmol) and DMF (25 mL). The resulting mixture was heated to 80-90 °C for 3 h and was then allowed to cool to 50 °C and stir overnight. The mixture was allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **90** as an orange oil which was used without purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, J= 9 Hz, 1H), 7.80-7.30 (br m, 2H), 7.08 (s, 1H), 7.03 (d, J= 6 Hz, 1H), 2.53 (s, 3H).

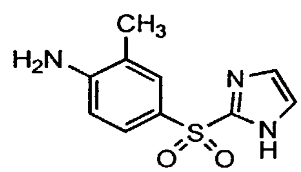
Step B:



91

Into a round-bottom flask were placed compound **90** (0.121 g, 0.51 mmol), glacial acetic acid (3 mL) and hydrogen peroxide (0.491 g of a 30% w/w solution, 4.33 mmol). The resulting mixture was heated to 85-90 °C for 2 h, after which time it was allowed to cool to rt and was poured into a flask containing a saturated solution of sodium bisulfite. The pH of the mixture was adjusted to pH 7 by the slow addition of solid $NaHCO_3$ and was then poured into a separatory funnel containing ethyl acetate. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **91** as a white solid (0.092 g, 67%). ^1H NMR (DMSO-d_6, 400 MHz) δ 8.16 (d, J= 8 Hz, 1H), 8.04 (s, 1H), 7.93 (d, J= 8 Hz, 1H), 7.35-7.32 (br m, 2H), 2.47 (s, 3H).

Step C:



92

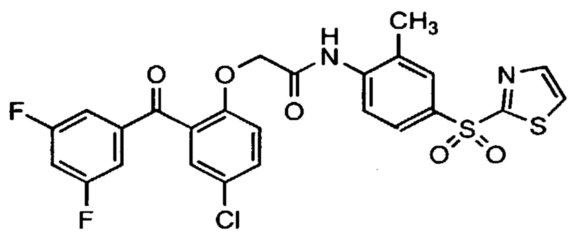
Into a Parr bottle were placed compound **91** (0.092 g, 0.34 mmol), Pd/C (0.01 g, 10% w/w), and ethanol. The bottle was purged with hydrogen (3X) and was finally pressurized to 40 psig. The mixture was allowed to stir at rt for 30 min, after which time the bottle was depressurized and the mixture was filtered through a pad of celite and the solvents were removed under reduced pressure to afford **92** as a yellowish solid (0.083 g, >100% yield), which was used without any further purification. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.54 (br s, 1H), 8.77 (s, 1H), 8.74 (s, 1H), 7.60 (dd, J= 8, 4 Hz, 1H), 7.45 (d, J= 4 Hz, 1H), 7.18 (br s, 2H), 7.09 (d, J= 8 Hz, 1H), 2.05 (s, 3H).

Step D:

Carboxylic acid **49** (0.100 g, 0.31 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and chloroform (3 mL) were used to prepared the acid chloride according to general procedure V. The acid chloride, amine **92** (0.065 g, 0.273 mmol), $NaHCO_3$ (0.134 g, 1.59 mmol), water (0.5 mL) and acetone (4 mL) were used according to general procedure VI to afford a tan solid. The solid was washed with several portions of ether and

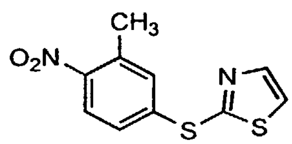
dried to afford **89** as a tan solid (0.105 g, 62%). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 13.74 (s, 1H), 10.26 (s, 1H), 7.70-7.27 (m, 10H), 6.95 (d, J= 9 Hz, 1H), 5.19 (s, 2H), 2.20 (s, 3H).

Example 38



93

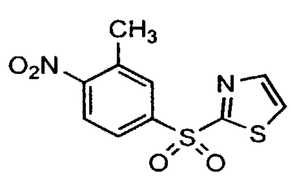
Step A:



94

Into a round-bottom flask were placed 5-fluoro-2-nitrotoluene (Lancaster, 1.65 g, 13.09 mmol), 2-thiothiazole (1.46 g, 12.46 mmol), K_2CO_3 (5.04 g, 36.47 mmol) and DMF (25 mL). The resulting mixture was heated to 80-90 °C for 3 h and was then allowed to cool to 50 °C and stir overnight. The mixture was allowed to cool to rt and was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and was washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **94** (2.51 g, 93%) as an orange solid which was used without purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, J= 8 Hz, 1H), 7.87 (d, J= 4 Hz, 1H), 7.44 (d, J= 4 Hz, 1H), 7.38-7.34 (m, 2H), 2.57 (s, 3H).

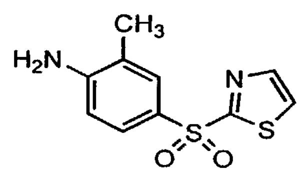
Step B:



95

Into a round-bottom flask were placed compound **94** (0.103 g, 0.41 mmol), glacial acetic acid (3 mL) and hydrogen peroxide (0.210 g of a 30% w/w solution, 1.85 mmol). The resulting mixture was heated to 85-90 °C for 2 h, after which time it was allowed to cool to rt and was poured into a flask containing a saturated solution of sodium bisulfite. The pH of the mixture was adjusted to pH 7 by the slow addition of solid $NaHCO_3$ and was then poured into a separatory funnel containing ethyl acetate. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **95** as a white solid (0.103 g, 89%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10-8.00 (m, 4H), 7.73 (d, J= 4 Hz, 1H), 2.64 (s, 3H).

Step C:



96

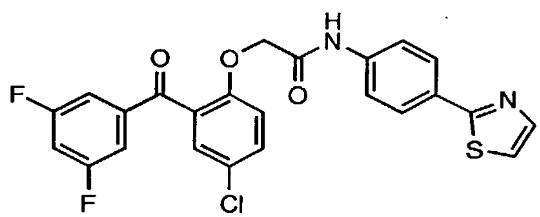
Into a Parr bottle were placed compound **95** (0.074 g, 0.34 mmol), Pd/C (0.018 g, 10% w/w), and ethanol (2 mL). The bottle was purged with hydrogen (3X) and was finally pressurized to 45 psig. The mixture was allowed to stir at rt for 30 min, after which time the bottle was depressurized and the mixture was filtered through a pad of celite and the solvents were removed under reduced pressure to afford **96** as a yellow oil, which was used without any further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, J= 3 Hz, 1H), 7.87 (d, J= 9 Hz, 1H), 7.74 (s, 1H), 7.65 (d, J= 3 Hz, 1H), 7.31 (d, J= 9 Hz, 1H), 5.81 (br s, 2H), 2.13 (s, 3H).

Step D:

Carboxylic acid **49** (0.104 g, 0.31 mmol), oxalyl chloride (0.6 mL of a 2.0 M solution in dichloromethane, 1.2 mmol), DMF (4 drops) and chloroform (4 mL) were used to prepared the acid chloride according to general procedure V. The acid chloride, amine **96** (0.071 g, 0.2793 mmol), $NaHCO_3$ (0.1434 g, 1.70 mmol), water (0.5 mL) and acetone (4 mL) were used according to general procedure VI to afford a tan solid. The solid was washed with several portions of ether and dried to afford **93** as a tan solid (0.129 g, 82%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.35 (s, 1H), 8.25 (d, J= 3 Hz, 1H), 8.09 (d, J= 3 Hz, 1H), 7.75-7.39 (m, 7H), 7.28 (d, J= 9 Hz, 1H), 6.97 (d, J= 9 Hz, 1H), 5.20 (s, 2H), 2.22 (s, 3H).

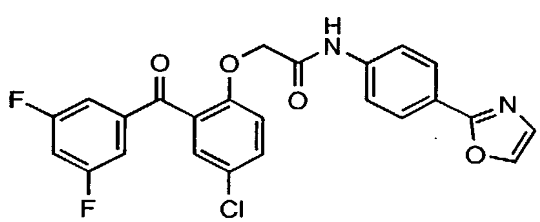
Example 39



97

Carboxylic acid 49 (0.108 g, 0.331 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and chloroform (3 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, the aniline (prepared according to the method of Erlenmeyer, *Helv. Chim. Acta*, 30, 2058-2060, 1947), 0.056 g, 0.318 mmol), $NaHCO_3$ (0.146 g, 1.74 mmol), water (0.5 mL) and acetone (6 mL) were used according to general procedure VI to provide 97 as a yellow solid (0.05 g, 32%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.19 (s, 1H), 7.95-7.90 (m, 3H), 7.76 (d, J= 3 Hz, 1H), 7.70-7.48 (m, 7H), 7.23 (d, J= 9 Hz, 1H), 4.80 (s, 2H).

Example 40

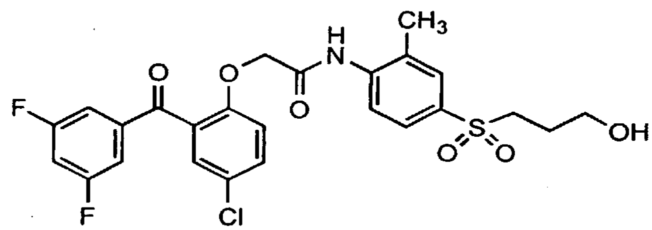


98

Carboxylic acid **49** (0.112 g, 0.343 mmol), oxalyl chloride (0.1 mL, 1.15 mmol), DMF (4 drops) and chloroform (3 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, the aniline (prepared according to the method of Brown, E.V., *Journal of Organic Chemistry*, 42(19), 3208-3209, 1977), 0.050 g, 0.312 mmol), $NaHCO_3$ (0.137 g, 1.63 mmol), water (0.5 mL) and acetone (6 mL) were used according to general procedure VI to provide **98** as a yellow solid (0.064 g, 44%). ^{1}H NMR (DMSO-

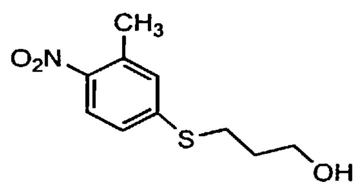
d_6, 300 MHz) δ 10.22 (s, 1H), 8.20 (s, 1H), 7.95 (d, J= 9 Hz, 1H), 7.72 (d, J= 9 Hz, 1H), 7.69-7.47 (m, 7H), 7.37 (s, 1H), 7.23 (d, J= 9 Hz, 1H), 4.81 (s, 2H).

Example 41



99

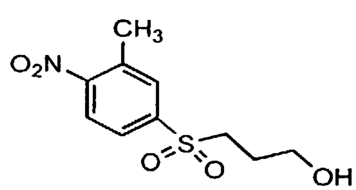
Step A:



100

Into a round-bottom flask were placed 5-fluoro-2-nitrotoluene (5.0 g, 32.2 mmol), K_2CO_3 (15.34 g, 111 mmol), 3-mercaptoethanol (3.2 mL, 37 mmol) and DMF (30 mL). The resulting mixture was allowed to stir at rt for 16 h, after which time it was poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **100** as thick, yellow oil, which was used without any further purification.

Step B:

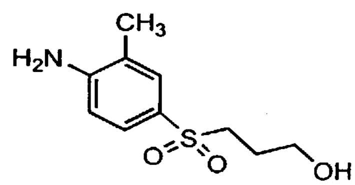


101

Into a round-bottom flask were placed compound **100** (~32 mmol), and methanol (100 mL). Into a separate flask were placed oxone (Aldrich, 29.43 g, 47.9 mmol) and water (125 mL). The oxone solution was added dropwise over several minutes to the solution of compound **100** at rt. The resulting solution was allowed to stir at rt for 1 h. It was then

poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected and washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a yellow oil, which was dried in vacuo to provide **101** as a yellow solid (7.91 g, 95%).

Step C:



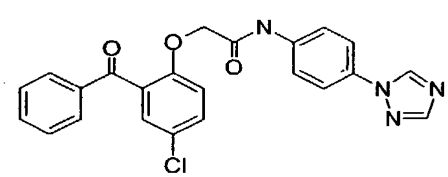
102

Into a Parr bottle were placed compound **101** (0.522 g, 2.01 mmol), Pd/C (0.04 g, 10% w/w) and EtOH (5 mL). The bottle was purged with hydrogen (3X) and was finally pressurized with hydrogen to 40 psig. The resulting mixture was allowed to stir at rt for 1 h, after which time it was filtered through a pad of celite, and the solvents were removed under reduced pressure to afford a green oil which solidified in vacuo to afford **102** as a yellowish solid (0.44 g, 95%).

Step D:

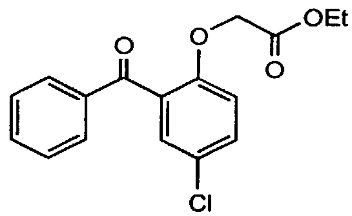
Carboxylic acid **49** (0.302 g, 0.924 mmol), oxalyl chloride (0.15 mL, 1.72 mmol), DMF (4 drops) and chloroform (10 mL) were used to prepare the acid chloride according to general procedure V. The acid chloride, amine **102** (0.190 g, 0.86 mmol), $NaHCO_3$ (0.323 g, 4.16 mmol), water (0.5 mL) and acetone (10 mL) were used according to general procedure X to provide **99** as a tan solid (0.326 g, 70%).

Example 43:



103

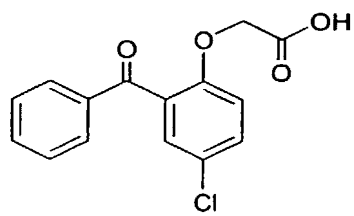
Step A:



104

This reaction was run according to general procedure II using 5-chloro-2-hydroxybenzophenone (15 g, 64 mmol), ethyl bromoacetate (7.7 mL, 71 mmol) and potassium carbonate and (44 g, 320 mmol). A 96% yield of **104** was obtained as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.8 (t, 3H), 4.1 (q, 2H), 4.8 (s, 2H), 7-7.8 (m, 8H).

Step B:



105

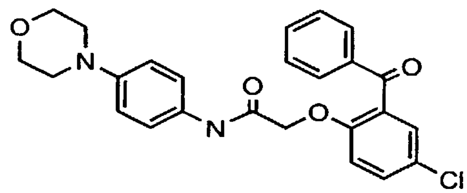
This reaction was run according to general procedure III using **104** (19.6 g, 62 mmol) and LiOH.H_2O (3.18 g, 76 mmol) in ethanol (250 mL) and water (70 mL) stirred for 1 h at rt. After extraction with methylene chloride, drying ($MgSO_4$) and solvent removal, an 86% yield of **105** was obtained as white foam. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.6 (s, 2H), 7-7.8 (m, 8H), 13 (s, 1H).

Step C:

A mixture of **105** (1 g, 3.4 mmol) and 18 mL of thionyl chloride was refluxed for 1 h. Concentration of the reaction mixture resulted in a crude product that was dissolved in acetonitrile. This was added dropwise to a stirred mixture of 1-(4'-aminophenyl)-1,2,4-triazole (0.54 g, 3.4 mmol) and triethylamine (0.73 mL, 5.25 mmol) in acetonitrile (10 mL). The mixture was refluxed for 6 h and stirred at rt for 24 h. Ethyl acetate was added to the reaction mixture. After washing with water, drying ($MgSO_4$) and solvent removal, the crude product was purified by flash column chromatography on silica with 4% methanol in methylene chloride as the eluent. This gave 0.039 g (3%) of **103** as a white

solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 7.2-7.8 (m, 12H), 8.2 (s, 1H), 9.2 (s, 1H), 10.0 (s, 1H).

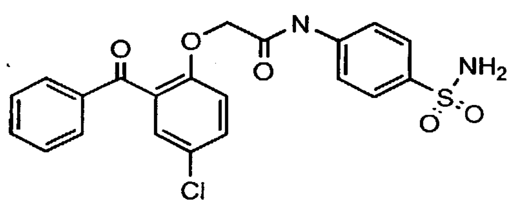
Example 44:



106

Following the procedure described for the synthesis of **103** and using 4-morpholinoaniline, a 38% yield of **106** was obtained as a gray solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 3 (s, 4H), 3.7 (s, 4H), 4.6 (s, 2H), 6.82 (m, 2H), 7.1-7.8 (m, 10H), 9.4 (s, 1H).

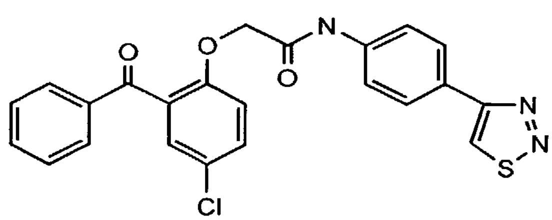
Example 45:



107

Following the procedure described for the synthesis of **103** and using sulfanilamide, a 6% yield of **107** was obtained as a white solid after purification by flash column chromatography on silica gel with 20% acetone in methylene chloride. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 6.82 (m, 2H), 7.1-7.8 (m, 12H), 10.1 (s, 1H).

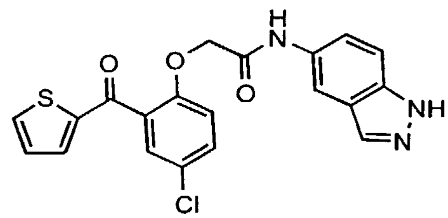
Example 46:



108

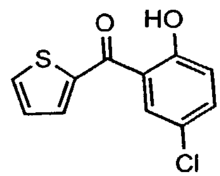
Following the procedure described for the synthesis of **103** and using 4-(4-aminophenyl)-1,2,3-thiadizole as the aniline, a 20% yield of **108** was obtained as a gray solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 7.2 (d, 1H), 7.4-8.1 (m, 112H), 9.41 (s, 1H), 10.0 (s, 1H).

Example 47:



109

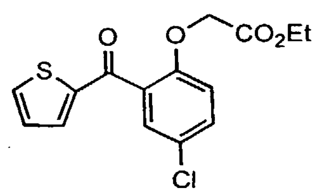
Step A:



110

This reaction was run according to general procedure I with 2-thiophenecarbonyl chloride (1.5 mL, 14 mmol), p-chloroanisole (1.7 mL, 14 mmol) and aluminum chloride (1.9 g, 14 mmol) were refluxed in methylene chloride (200 mL) for 24 h. A 39% yield of **110** was obtained after purification by flash column chromatography on silica gel with methylene chloride/hexane (1:1). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.95 (d, 1H), 7.19 (t, 1H), 7.32 (d, 1H), 7.38 (dd, 1H), 7.51 (d, 1H), 8.06 (d, 1H), 10.3 (s, 1H).

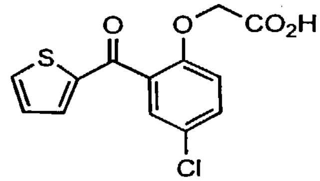
Step B:



111

This reaction was run according to general procedure II using **110** (0.5 g, 2.17 mmol), ethyl bromoacetate (0.24 mL, 2.17 mmol) and potassium carbonate (1.53 g, 10.85 mmol), in acetone (25 mL) for 3 h. A 97% yield of **111** was obtained as oil after workup. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.1 (t, 3H), 4.1 (q, 2H), 4.8 (s, 2H), 7.07 (d, 1H), 7.19 (t, 1H), 7.43 (d, 1H), 7.49-7.52 (m, 2H), 8.07 (d, 1H).

Step C:



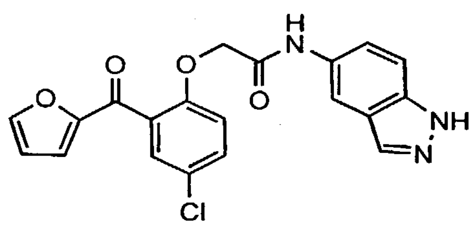
112

Following the procedure described in general procedure III, a 22% yield of **112** was obtained as a solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 7.05 (d, 1H), 7.18 (t, 1H), 7.41 (d, 1H), 7.42-7.6 (m, 2H), 8.06 (d, 1H).

Step D:

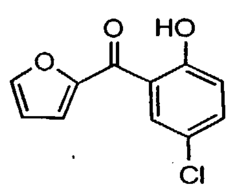
This reaction was run according to general procedure IV using **112** (0.14 g, 0.43 mmol), HOBT (0.06 g, 0.43 mmol), 5-aminoindazole(0.06 g, 0.43 mmol), EDAC (0.08 g, 0.43 mmol) and triethylamine (0.12 mL, 0.86 mmol). A 23% yield of **109** was obtained after purification by flash column chromatography on silica gel with 5% methanol in methylene chloride. ^{1}H NMR (DMSQ-d_6, 300 MHz) δ 4.8 (s, 2H), 7.1-7.3 (m, 2H), 7.32 (d, 1H), 7.46 (d, 1H), 7.48 (s, 1H), 7.56 (d, 1H), 7.7 (d, 1H), 7.98 (s, 1H), 8.04 (s, 1H), 8.1 (d, 1H), 9.8 (s, 1H), 13 (s, 1H).

Example 48:



113

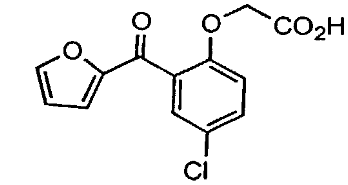
Step A:



114

Following the procedure described in generl procedure I using 2-furoyl chloride and p-chloroanisole, a 73% yield of **114** was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.7 (m, 1H), 6.93 (d, 1H), 7.2 (2, 1H), 7.4 (m, 2H), 8.04 (s, 1H), 10.4 (1H).

Step B:



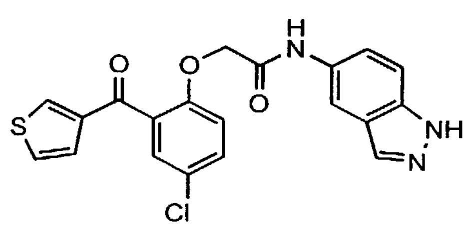
115

A mixture of **114** (1 g, 4.49 mmol), ethyl bromoacetate (0.5 mL, 4.49 mmol) and potassium carbonate (3.17 g, 22.45 mmol) was stirred in acetone (50 mL) for 24 h. To this was added 1N NaOH until the solid dissolved. This NaOH solution was extracted once with ethyl acetate and was then acidified with 1N HCl. This was followed by extraction with ethyl acetate. After drying ($MgSO_4$) and solvent removal in vacuo, the crude product was re-crystallized with hexane/ethyl acetate. Compound **115** (1 g, 79%) was collected as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.8 (s, 2H), 6.7 (m, 1H), 7.1 (d, 1H), 7.2 (d, 1H), 7.5 (m, 1H), 7.6 (d, 1H), 8.1 (s 1H), 13.1 (br s, 1H).

Step C:

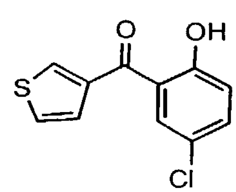
Following the procedure described in general procedure IV using 5-indazole, a 61% yield of **113** was obtained as a solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.8 (s, 2H), 6.8 (m, 1H), 7.21 (d, 1H), 7.3-7.7 (m, 5H), 8.06 (s, 1H), 8.1 (s, 2H), 10 (s, 1H), 13 (s, 1H).

<u>Example 49:</u>



116

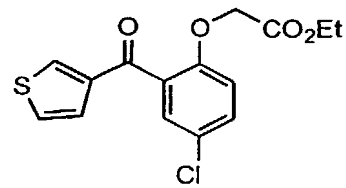
Step A:



117

A mixture of 3-thiophenecarboxyl in acid (3.58 g, 28 mmol) and thionyl chloride (15 mL) was refluxed for 3 h. The reaction mixture was concentrated and further dried in vacuo. The resultant concentrate was added to a suspension of aluminum chloride (7.61g, 56 mmol) and p-chloroanisole (3.41 mL, 28 mmol). The suspension was heated to reflux for 24 h. Water was slowly added to the reaction mixture and this aqueous mixture was extracted with first methylene chloride, then ethyl acetate. The organic solutions were combined and dried over $MgSO_4$. After solvent removal, the crude product was purified by flash column chromatography on silica gel with methylene chloride/hexane (1:1). This gave 0.13 g (2%) of **117** as oil. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7 (d, 1H), 7.3-7.5 (m, 3H), 7.6-7.7 (m, 1H), 8.2 (m, 1H), 10.4 (s, 1H).

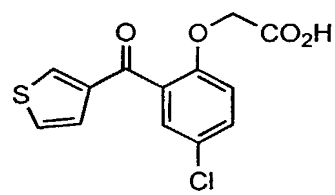
Step B:



118

Following general procedure II, a 45% yield of **118** was obtained as oil. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.1 (t, 3H), 4.08 (q, 2H), 4.8 (s, 2H), 7.07 (d, 1H), 7.38 (d, 1H), 7.44 (d, 1H), 7.49 (dd, 1H), 7.6 (dd, 1H), 8.11 (d, 1H).

Step C:



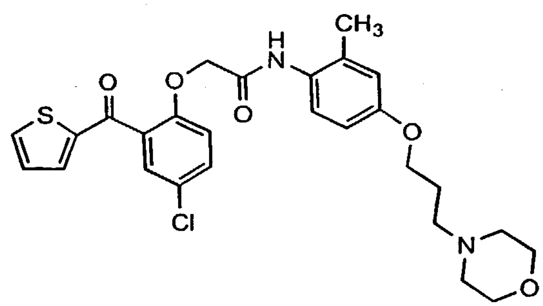
119

Following general procedure III, a 67% yield of **119** was obtained as oil. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 7.1 (d, 1H), 7.38 (d, 1H), 7.5-7.6 (m, 2H), 7.6-7.7 (m, 1H), 8.2 (m 1H).

Step D:

Following general procedure IV using 5-indazole, a 36% yield of **116** was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.8 (s, 2H), 7.2 (d, 1H), 7.35 (d with fine splittings, 1H), 7.42 (d, 1H), 7.45 (d, 1H), 7.5-7.6 (m, 2H), 7.6-7.65 (m, 1H), 8 (s, 1H), 8.05 (s, 1H), 8.3 (m, 1H), 9.8 (s, 1H), 13 (s, 1H).

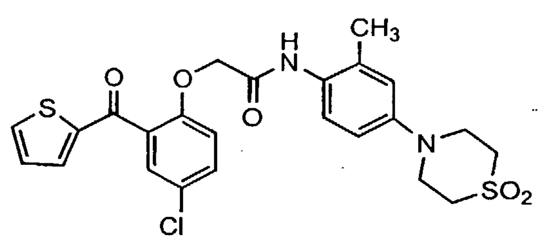
Example 50:



120

Following general procedure IV using 4-(3-morpholino)propyloxy-2-methylaniline, a 7% yield of **120** was obtained as a white solid after flash column chromatography on silica gel with 20% methanol in methylene chloride. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.9 (m, 2H), 2 (s, 3H), 2.2-2.4 (m, 6H), 3.5-3.6 (m, 4H), 3.9 (t, 2H), 4.75 (s, 2H), 6.7 (d, 1H), 6.74 (s, 1H), 7.1-7.3 (m, 3H), 7.5 (s, 1H), 7.6 (dd, 1H), 7.63 (d, 1H), 8.08 (d, 1H), 9 (s, 1H).

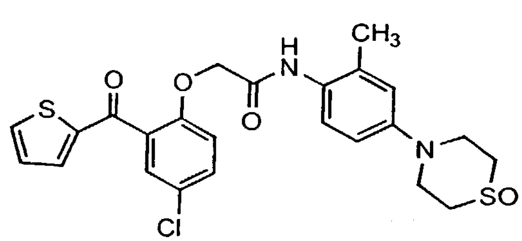
Example 51:



121

Following general procedure IV using 4-morpholinesulfonyl-2-methylaniline, a 26% yield of **121** was obtained as a white solid after flash column chromatography on silica gel with 20% methanol in methylene chloride. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.1 (br s, 4H), 3.7 (s, 4H), 4.8 (s, 2H), 7 (d, 2H), 7.2-7.3 (m, 2H), 7.43 (d, 2H), 7.54 (d, 1H), 7.6 (dd, 1H), 7.7 (d, 1H), 8.2 (d, 1H), 9.8 (s, 1H).

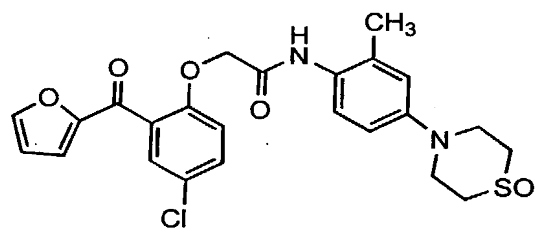
Example 52:



122

Following general procedure IV using 4-morpholinesulfonyl-2-methylaniline, a 24% yield of **122** was obtained as a white solid after flash column chromatography on silica gel with 5% methanol in methylene chloride. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.6-2.8 (m, 2H), 2.9 (t, 2H), 3.5-3.6 (m, 2H), 3.7 (t, 2H), 4.8 (s, 2H), 7 (d, 2H), 7.2-7.3 (m, 2H), 7.43 (d, 2H), 7.54 (d, 1H), 7.6 (dd, 1H), 7.7 (d, 1H), 8.2 (d, 1H), 9.8 (s, 1H).

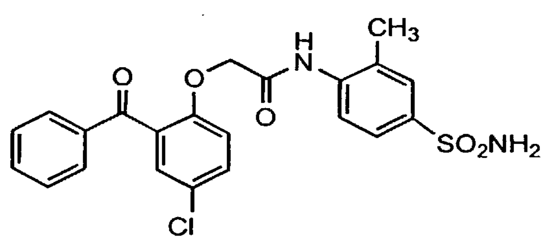
Example 53:



123

Following general procedure IV, a 35% yield of **123** was obtained as a white solid after flash column chromatography on silica gel with 3% methanol in methylene chloride. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.0 (s, 3H), 2.5-2.7 (m, 2H), 2.9 (t, 2H), 3.5-3.6 (m, 2H), 3.7 (t, 2H), 4.8 (s, 2H), 6.7 (s, 1H), 6.78 (d, 1H), 6.8 (s, 1H), 7.1-7.3 (m, 2H), 7.3 (d, 1H), 7.5 (d, 1H), 7.6 (dd, 1H), 8.05 (s, 1H), 9 (s, 1H).

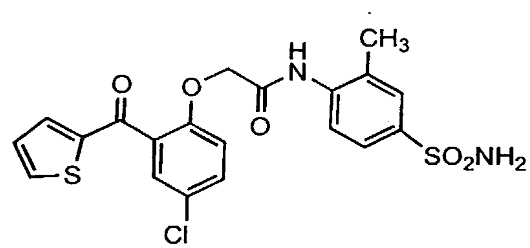
Example 54:



124

Following general procedure IV, a 32% yield of **124** was obtained as a white solid after flash column chromatography on silica gel with 5% methanol in methylene chloride. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.1 (s, 3H), 4.8 (s, 2H), 71.-7.3 (m, 3H), 7.4 (s with fine splittings, 1H), 7.42-7.5 (m, 2H), 7.5-7.7 (m, 5H), 7.8 (d, 2H), 9.2 (s, 1H).

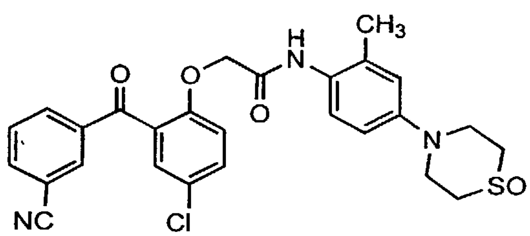
Example 55:



125

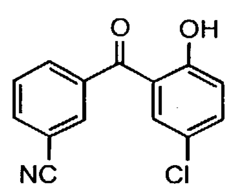
Following the procedure described for the synthesis of compound **103**, a 42% yield **125** was obtained as a white solid after flash column chromatography on silica gel with 3% methanol in methylene chloride. ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 2.2 (s, 3H), 4.8 (s, 2H), 7.1-7.3 (m, 3H), 7.5 (d, 1H), 7.5-7.7 (m, 5H), 7.73 (d, 1H), 8.1 (d, 1H), 9.3 (s, 1H).

Example 56:



126

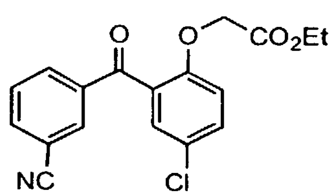
Step A:



127

Following general procedure I, a 9% yield of **127** was obtained after flash column chromatography on gel with 30% hexane in methylene chloride. ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 6.97 (d, 1H), 7.38 (s, 1H), 7.42 (d, 1H), 7.7 (t, 1H), 7.98 (d, 1H), 8-8.1 (m, 2H), 10.4 (s, 1H).

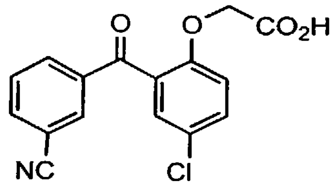
Step B:



128

Following general procedure II, a quantitative yield of **128** was obtained as oil that was used in the following reaction without any additional purification.

Step C:



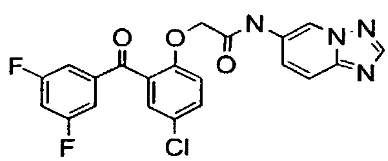
129

Following general procedure III, a quantitative yield of **129** was obtained as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 4.6 (s, 2H), 7.1 (d, 1H), 7.5 (s, 1H), 7.5-7.6 (m, 1H), 7.6-7.7 (m, 1H), 8-8.1 (m, 2H), 12 (br s, 1H).

Step D:

Following general procedure IV, an 11% yield of **126** was obtained as a yellow solid after flash column chromatography on silica gel with 4% methanol in methylene chloride. ^1H NMR (DMSO-d_6, 300 MHz) δ 2.0 (s, 3H), 2.5-2.7 (m, 2H), 2.9 (t, 2H), 3.5-3.6 (m, 2H), 3.7 (t, 2H), 4.7 (s, 2H), 6.7 (d, 1H), 6.8 (s, 1H), 7.1 (d, 1H), 7.2 (d, 1H), 7.5 (d, 1H), 7.6-7.7 (m, 2H), 8-8.1 (m, 2H), 8.2 (s, 1H), 9 (s, 1H).

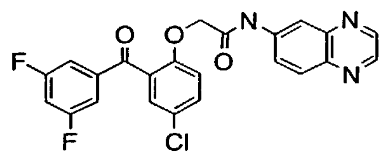
<u>**Example 57**</u> :



130

Acid **49** (0.1 g, 0.3 mmole), was converted to the acid chloride by reaction with oxalyl chloride (0.1 mL, 0.8 mmol) in dichloromethane (5 mL) and 1 drop of DMF (Aldrich, Sure Seal). The reaction was stirred at rt for 1 h. The solvent was removed in vacuo. The title compound was prepared by addition of the acid chloride to 6-amino-s-triazolo(1,5-a)pyridine (0.04 g, 0.3 mmol; prepared by the method of Potts, K. T. and Surapaneni, C. R., J. Heterocyclic Chem., 1970, 7, 1019) and sodium bicarbonate (0.2 g, 2.2 mmol) in acetone (10 mL) and water (1 mL) by general procedure VI. The product was isolated by chromatography on silica gel eluted with chloroform/methanol (95:5, v/v) in 15% yield. MS (ES(+)): m+1/z 443. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.85 (s, 1H), 9.66 (s, 1H), 8.32 (s, 1H), 7.79 (m, 2H), 7.57 (dd, 1H), 7.4 (m, 3H), 7.15-7.05 (m, 2H), 4.79 (s, 2H).

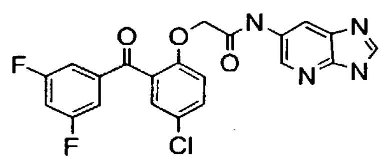
Example 58:



131

Acid **49** (0.1 g, 0.3 mmol), was converted to the acid chloride by reaction with oxalyl chloride (0.1 ml, 0.8 mmol) in dichloromethane (5 mL) and 1 drop of DMF (Aldrich, Sure Seal). The reaction was stirred at rt for 1 h. The solvent was removed in vacuo. The title compound was prepared by addition of the acid chloride to 6-aminoquinoxaline (0.045 g, 0.3 mmol; prepared by the method of Case, F. H. and Brennan, J. A., JACS, 1959, 81, 6297) and sodium bicarbonate (0.2 g, 2.2 mmol) in acetone (10 mL) and water (1 mL) by general procedure VI. The product was isolated by chromatography on silica gel eluted with chloroform/methanol (95:5, v/v) in 15% yield. MS (ES(+)): m+1/z 454. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 (s, 1H), 8.82 (s, 1H), 8.76 (s, 1H), 8.64 (s, 1H), 8.18 (dd, 1H), 8.09 (d, 1H), 7.56 (dd, 1H), 7.6 (m, 3H), 7.15-7.05 (m, 2H), 4.79 (s, 2H).

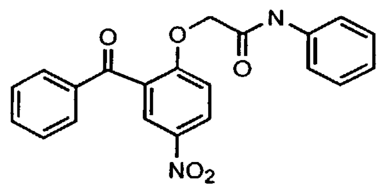
Example 59:



132

Acid **49** (0.1 g, 0.3 mmol), was converted to the acid chloride by reaction with oxalyl chloride (0.1 mL, 0.8 mmol) in dichloromethane (5 mL) and 1 drop of DMF (Aldrich, Sure Seal). The reaction was stirred at rt for 1 h. The solvent was removed in vacuo. The title compound was prepared by addition of the acid chloride to 6-amino-1H-imidazo[4,5-b]pyridine (0.04 g, 0.3 mmol; which can be prepared by the method of Brooks, W. and Day, A. R., J. Heterocyclic Chem., 1969, 6(5), 759) and sodium bicarbonate (0.2 g, 2.2 mmol) in acetone (10 mL) and water (1 mL) by general procedure VI. The product was isolated by chromatography on silica gel eluted with chloroform/methanol (9:1, v/v) in 10% yield. MS (ES(+)): m+1/z 443. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.66 (s, 1H), 8.83 (s, 1H), 8.66 (s, 1H), 8.28 (s, 1H), 7.58 (dd, 1H), 7.4 (m, 3H), 7.15-7.05 (m, 2H), 4.79 (s, 2H).

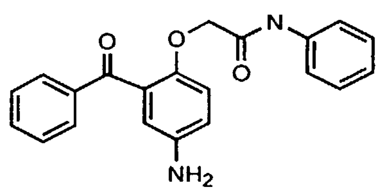
Example 60:



133

2-Hydroxy-5-nitrobenzophenone (1.09 g, 4.50 mmol, which can be prepared by the method of Hayashi, I. *et.al.*, Bull.Chem. Soc. Jpn., 1983, 56(8), 2432-7), 2-bromo-N-phenyl acetamide (1.01 g, 4.74 mmol, which can be prepared by the method of Vloon, W. *et.al.*, J.Med.Chem., 1987, 30, 20-24), and potassium carbonate (656 mg, 4.74 mmol) were added to DMF (20 mL). The reaction was stirred for 16 h at rt. The reaction was poured onto ice water and a precipitate formed. The precipitate was filtered and rinsed with water. The product was purified by chromatography on silica gel using a Biotage flash chromatography system, eluting with hexane/ethyl acetate (3:1) to obtain 1 g (2.66 mmol, 59% yield). MS (ES(+)): m+1/z 377, MS (ES(-)): m-1/z 375. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.96 (s, 1H), 8.46 (dd, 1H), 8.36 (d, 1H), 7.90 (d, 2H), 7.66 (m, 3H), 7.55 (m, 2H), 7.34 (t, 2H), 7.19 (d, 1H), 7.13 (t, 1H), 4.79 (s, 2H).

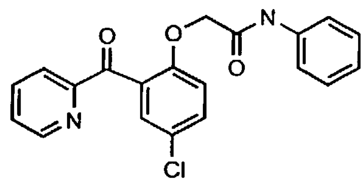
Example 61:



134

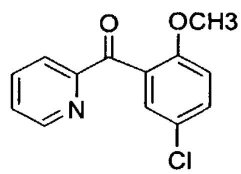
Compound **133** (50 mg, 133 mmol) and Raney-Nickel catalyst (Aldrich, 45 mg, 90% by weight) were added to ethanol (30 mL) and placed on a Parr hydrogenator at 50 psig hydrogen pressure. Additional catalyst (100 mg) was added at 1 h intervals. After 3 h, the catalyst was filtered and the solvents removed in vacuo. The product was purified by chromatography on silica gel eluted with chloroform/methanol (98:2) to obtain 38.6 mg (112 mmol, 84% yield). MS (ES(+)): m+1/z 347. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.06 (s, 1H), 7.90 (d, 2H), 7.60 (m, 3H), 7.48 (m, 2H), 7.30 (t, 2H), 7.09 (t, 1H), 6.90 (d, 1H), 6.84 (dd, 1H), 6.74 (d, 1H), 4.59 (s, 2H), 3.62 (br s, 2H).

Example 62:



135

StepA:



136

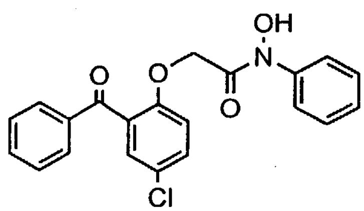
2-Bromo-4-chloroanisole (24.4 g, 0.11 mol) was added dropwise to a stirred suspension of magnesium (2.7 g, 0.11 mol) in diethyl ether (150 mL) containing a crystal of iodine. The mixture was heated to reflux for 2 h. A solution of 2-cyanopyridine (11.4 g, 0.11 mol) in diethyl ether (100 mL) was added dropwise and the resulting suspension (yellowish-tan precipitate formed) was refluxed for 2h, cooled to rt and poured into cold 2N HCl (300 mL). The diethyl ether layer was separated and discarded. The aqueous layer was made basic by addition of 50% aq NaOH and extracted with ether (4 x 300 mL). The combined ether extracts were washed with water, dried over sodium sulfate, and evaporated to give a brown solid. The product was purified by chromatography on silica gel eluted with ethyl acetate/hexane (1:3) to give 10.9 g, in 40% yield. MS (ES^+) m/z: 248.0 (M+1, 85%), 270 (M+23, 45%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (d, 1H), 8.02 (d, 1H), 7.85 (t, 1H), 7.41-7.47 (m, 3H), 6.91 (d, 1H), 3.64 (s, 3H).

Step B:

1-(5-Chloro-2-methoxyphenyl)-1-(2-pyridinyl) methanone (125 mg, 0.505 mmol) was dissolved in dichloromethane (5 mL) and chilled to –78°C in a dry ice/acetone bath. A nitrogen atmosphere was provided. Boron tribromide (1M in CH_2Cl_2, 2 mL, 2 mmol) was added dropwise and the flask warmed to rt overnight. Water (5 mL) was added dropwise, and the contents of the flask were washed once with water, once with brine, dried over sodium sulfate, and solvents removed in vacuo. The crude sample was dissolved in DMF (5 mL). 2-Bromo-N-phenyl acetamide (113 mg, 0.532 mmol, which can be prepared by

the method of Vloon, W. *et.al.*, J.Med.Chem., 1987, 30, 20-24) and potassium carbonate (73.5 mg, 0.532 mmol) were added. After 64 h the contents of the flask were poured onto ice water (50 mL) and the precipitate was filtered. The product was purified by chromatography on silica gel using a Biotage flash chromatography system, eluting with hexane/ethyl acetate (3:1) to obtain 15.5 mg (42.3 mmol, 8.4% yield over two steps). MS (ES(+)): m+1/z 367. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.38 (s, 1H), 8.60 (d, 1H), 8.20 (d, 1H), 7.93 (td, 1H), 7.60 (m, 3H), 7.47 (m, 2H), 7.33 (t, 2H), 7.12 (t, 1H), 6.94 (d, 1H), 4.63 (s, 2H).

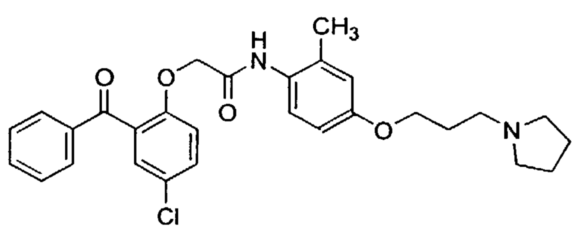
Example 63:



137

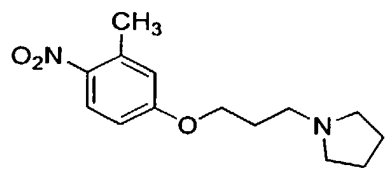
2-(2-Benzoyl-4-chlorophenoxy)acetyl chloride (0.1 g, 0.32 mmol was dissolved in dry acetonitrile (2 mL). 2-Phenylhydroxylamine (which was prepared by the method outlined in Org. Syn. Col. Vol. I, p.445, 0.35g) was dissolved in ether and dried with $MgSO_4$. The mixture was filtered and the ether removed in vacuo. The residue was dissolved in acetonitrile (2 mL) and added to the acid chloride solution. The reaction was stirred at rt for 3 h. A precipitate formed and was filtered. The reaction solvent was removed in vacuo. The product was purified by chromatography on silica gel eluted with hexane/ethyl acetate (3:1, v/v). The product containing fractions were combined and the solvents removed in vacuo to provide a 50% yield. MS (APCI(+)): m+Na/z 404. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.85 (s, 1H), 7.85 -7.0(m, 13H), 4.95 (s, 2H).

Example 64:



138

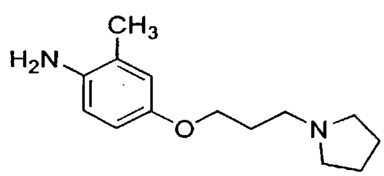
Step A:



139

4-(3-bromopropoxy)-2-methyl-1-nitrobenzene (8.0 g, 29.2 mmol, which can be prepared according to the method found in Patent; Wellcome Foundation; GB 982572; 1960; Chem.Abstr.; EN; 63; 2928b; 1965), pyrrolidine (92.5 mL, 29.2 mmol) and K_2CO_3 (5.0 g, 35 mmol) were mixed together in DMF (30 mL) at rt for 16 h. The reaction mixture was filtered and the solvents were removed under reduced pressure to leave an oil and was dissovled in CH_2Cl_2, washed with aqueous NaOH (1N), water, dried and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 95:5 dichloromethane/methanol as eluant to afford **139** as an orange oil (7.5 g, 97%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.84 (m, 4H), 2.06 (ddd, 2H), 2.57 (m, 6H), 2.58 (s, 3H), 4.14 (t, 2H), 6.84 (m, 3H), 8.10 (d, 1H).

Step B:



140

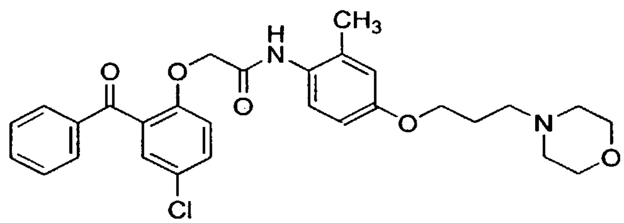
Into a stirred Parr bottle were placed compound **139** (7.5 g, 28.4 mmol), Pd/C (0.75 g, 10%), and EtOH (300 mL). The bottle was pressurized to 5 atm. with hydrogen gas and was allowed to stir at rt for 3 h. The mixture was then filtered through a pad of celite and the solvents were removed under reduced pressure to give **140** as an orange oil (6.0 g, 98%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.84 (m, 4H), 1.98 (ddd, 2H), 2.19 (s, 3H), 2.42 (m, 6H), 3.28 (br s, 1H), 3.98 (t, 2H), 6.84 (m, 3H).

Step C:

Carboxylic acid **105** (1.0 g, 3.9 mmol), amine **140** (1.22 g, 3.9 mmol), HOBt (5.25 g, 3.9 mmol), EDAC (0.9 g, 4.7 mmol), triethylamine (1.3 mL, 3.9 mmol) and DMF (50 mL) were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol as eluant to provide **138** as an

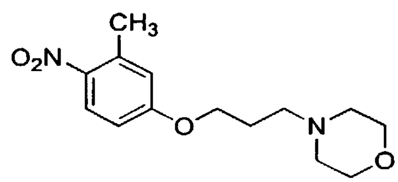
orange oil (0.84 g, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 3H), 2.11 (m, 6H), 2.30 (ddd, 2H), 3.22 (m, 4H), 4.01 (t, 2H), 4.63 (s, 2H), 6.65 (m, 2H), 7.01-7.55 (m, 6H), 7.79 (dd, 2H), 7.98 (s, 1H), 8.13 (s, 1H).

Example 65:



141

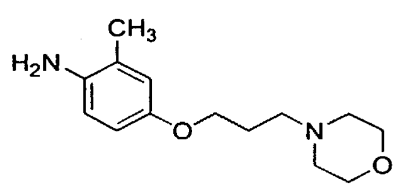
Step A:



142

4-(3-bromopropoxy)-2-methyl-1-nitrobenzene, and morpholine (5.0 g, 18.2 mmol) were used in the same manner as to prepare compound **139**. Compound **142** was obtained as an oil (5.1 g, 100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02 (ddd, 2H), 2.38 -2.56 (m, 6H), 2.64 (s, 3H), 3.73 (m, 4H), 4.11 (t, 2H), 6.81 (m, 2H), 8.09 (d, 1H).

Step B:



143

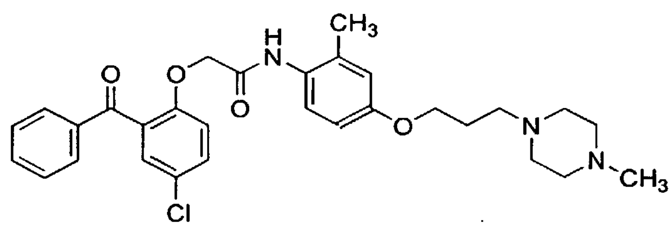
Compound **142** (5.1 g, 18.2 mmol) was used in the same manner as that to prepare compound **140**. Amine **143** was obtained as an oil (4.3 g, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.94 (ddd, 2H), 2.19 (s, 3H), 2.49-2.54 (m, 6H), 3.39 (br s, 1H), 3.75 (m, 4H), 3.96 (t, 2H), 6.64-6.70 (m, 3H).

Step C:

Carboxylic acid **105**, amine **143**, HOBt, EDAC, triethylamine, and DMF were used according to general procedure IV. The product was purified by flash chromatography

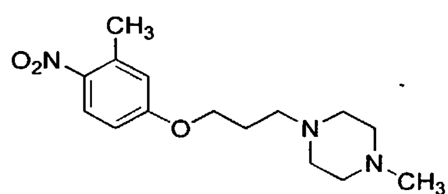
using 95:5 dichloromethane/methanol to afford **141** as an oil (1.3 g, 67%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.98 (ddd, 2H), 2.11 (s, 3H), 2.48-2.56 (m, 6H), 3.75 (m, 4H), 4.02 (t, 2H), 4.68 (s, 2H), 6.6-7.37 (m, 9H), 7.86 (d, 2H), 8.11 (s, 1H).

Example 66:



144

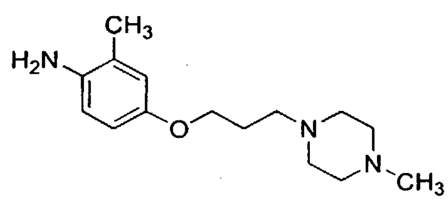
Step A:



144

4-(3-bromo-propoxy)-2-methyl-1-nitro-benzene, and 1-methylpiperazine (5.0 g, 18.2 mmol) were used in the same manner as to prepare compound **139**. Compound **144** was obtained as an oil (3.4 g, 63%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.98 (ddd, 2H), 2.26 (s, 3H), 2.38-2.60 (m, 10H), 2.65 (s, 3H), 4.11 (t, 2H), 6.80 (m, 2H), 8.10 (d, 1H).

Step B:



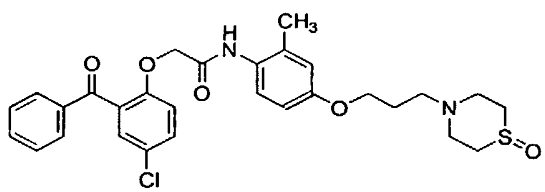
145

Compound **144** (3.4 g, 12.5 mmol) was used in the same manner as that to prepare compound **140**. Amine **145** was obtained as an oil (3.1 g, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88 (ddd, 2H), 2.10 (s, 3H), 2.25 (s, 3H), 2.26-2.65 (m, 10H), 3.35 (br s, 1H), 3.89 (t, 2H), 6.50-6.70 (m, 3H).

Step C:

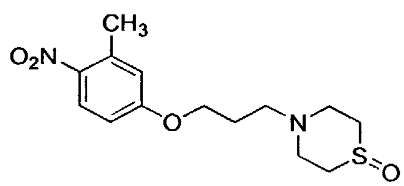
Carboxylic acid **105**, amine **145**, HOBt, EDAC, triethylamine, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **144** as an oil (0.95 g, 47%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.92 (m, 2H), 2.05 (s, 3H), 2.29 (s, 3H), 2.40-2.70 (m, 10H), 3.39 (s, 1H), 3.95 (t, 2H), 4.62 (s, 2H), 6.70 (s, 2H), 6.90 (d, 1H), 6.72-7.60 (m, 5H), 7.81 (d, 2H), 8.06 (s, 1H).

Example 67:



146

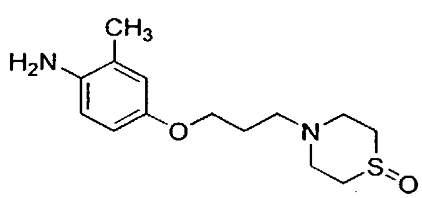
Step A:



147

4-(3-bromo-propoxy)-2-methyl-1-nitro-benzene, and thiomorpholine-1-oxide (5.0 g, 18.2 mmol, which can be prepared according to Nachtergaele, Willy A.; Anteunis, Marc J. O.; Bull.Soc.Chim.Belg.; EN; 89; 7; 1980; 525-536) were used in the same manner as to prepare compound **139**. Compound **147** was obtained as an oil (2.1 g, 37%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (ddd, 2H), 2.65 (s, 3H), 2.63 (t, 2H), 2.65-3.20 (m, 8H), 4.12 (t, 2H), 6.82 (m, 2H), 8.10 (s, 1H).

Step B:



148

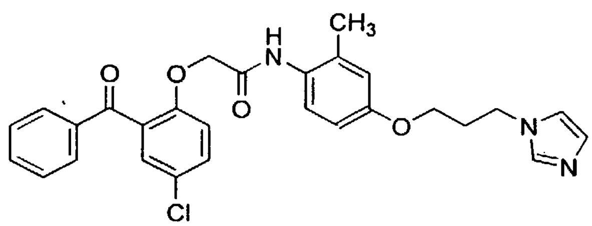
Compound **147** (2.1 g, 6.7 mmol) was used in the same manner as that to prepare compound **140**. Amine **148** was obtained as an oil (2.1 g, 98%). ^{1}H NMR ($CDCl_3$, 300

MHz) δ 1.84 (ddd, 2H), 2.15 (s, 3H), 2.58 (t, 2H), 2.65-3.25 (m, 10H),3.84 (t, 2H), 6.28 (m, 3H).

Step C:

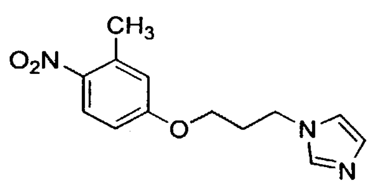
Carboxylic acid **105**, amine **148**, HOBt, EDAC, triethylamine, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **146** as an oil (0.7 g, 32%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95 (ddd, 2H), 2.71 (s, 3H), 2.63 (t, 2H), 2.65-3.20 (m ,8H), 4.00 (t, 2H), 4.67 (s, 2H), 6.72 (s, 2H), 7.03 (d, 2H), 7.38-7.85 (m, 6H), 7.85 (m, 2H), 8.15 (s, 1H).

<u>Example 68:</u>



149

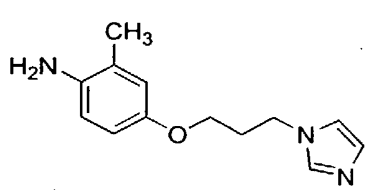
Step A:



150

4-(3-bromo-propoxy)-2-methyl-1-nitro-benzene, and imidazole (5.0 g, 18.2 mmol) were used in the same manner as to prepare compound **139**. Compound **150** was obtained as an oil (3.1 g, 61%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (ddd, 2H), 2.66 (s, 3H), 3.64 (d, 2H), 4.00 (d, 2H), 6.8 (s, 2H), 6.95 (d, 2H), 7.11 (d, 2H), 7.53 (s, 1H), 8.10 (d, 1H).

Step B:



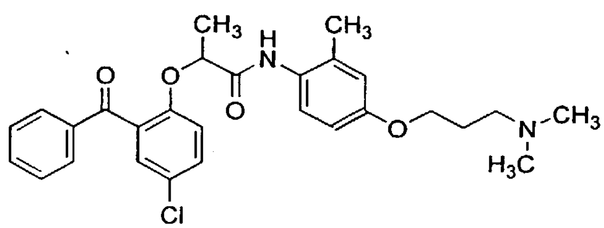
151

Compound **150** (3.1 g) was used in the same manner as that to prepare compound **140**. Amine **148** was obtained as an oil (0.71 g, 26%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (ddd, 2H), 2.18 (s, 3H), 3.88 (t, 2H), 4.06 (br s, 1H), 4.25 (t, 2H), 6.60 (m, 3H), 6.98 (d, 2H), 7.13 (d, 2H), 7.13 (d, 2H), 7.82 (s, 1H).

Step C:

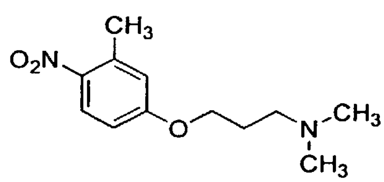
Carboxylic acid **105**, amine **151**, HOBt, EDAC, triethylamine, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **149** as an oil (1.1 g, 51%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (ddd, 2 H), 2.18 (s, 3H), 3.80 (t, 2H), 4.18 (t, 2H), 4.63 (s, 2H), 6.60-7.62 (m, 8H), 7.82 (d, 2H), 8.18 (s, 1H).

__Example 69:__



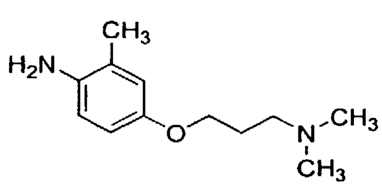
152

Step A:



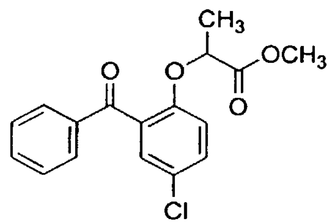
153

Step B:



154

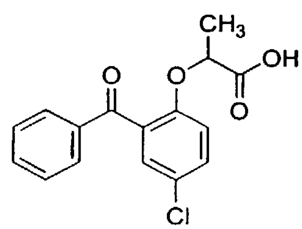
Step C:



155

A mixture of 5-chloro-2-hydroxybenzophenone (25 g, 107.4 mmol), methyl 2-bromopropionate, K_2CO_3 (23.0 g, 161 mmol) and acetone (250 mL) were used according to general procedure II to afford **155** as a yellow oil (32.0 g, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (d, 3H), 3.64 (s, 3H), 4.62 (q, 1H), 6.78 (d, 1H), 7.22-7.61 (m, 5H).

Step D:



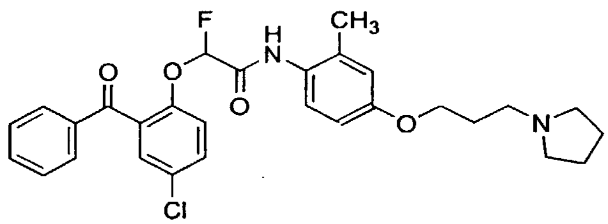
156

Ester **155** (11 g, 34.5 mmol), water (5 mL) and ethanol (150 mL) were used according to general procedure III, except that sodium hydroxide (5 mL of a 5N solution, 25 mmol) was used in place of lithium hydroxide. Acid **156** was obtained as a brown oil (4.5 g, 43%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65 (d, 3H), 4.96 (q, 1H), 7.10-7.98 (m, 8H).

Step E:

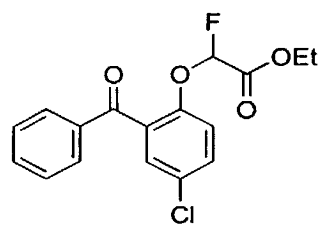
Carboxylic acid **156**, amine **154** (0.68 g, 3.3 mmol), EDAC, HOBt and DMF were used according to general procedure IV to afford compound **152** as an orange oil (1.1 g, 61%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.6 (d, 3H), 1.95 (ddd, 2H), 2.05 (s, 3H), 2.26 (s, 6H), 2.45 (t, 2H), 3.88 (t, 2H), 4.92 (q, 1H), 6.64 (m, 9H), 7.84 (d, 2H), 8.22 (s, 1H).

<u>**Example 70:**</u>



157

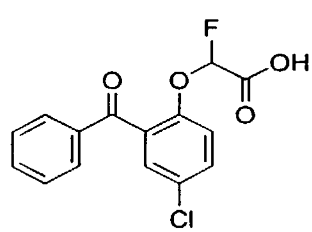
Step A:



158

A mixture of 5-chloro-2-hydroxybenzophenone (6.3 g, 27 mmol), ethyl bromofluoroacetate, K_2CO_3 (4.5 g, 32 mmol) and DMF (50 mL) were combined and the reaction mixture was allowed to stir at 80 °C for 24 h. The mixture was then filtered, and poured into a separatory funnel containing ethyl acetate and water. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **158** as an oil (7.0 g, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H), 4.17 (q, 2H), 5.66 (d, 1H), 5.87 (d, 1H), 7.19-8.82 (m, 8H).

Step B:



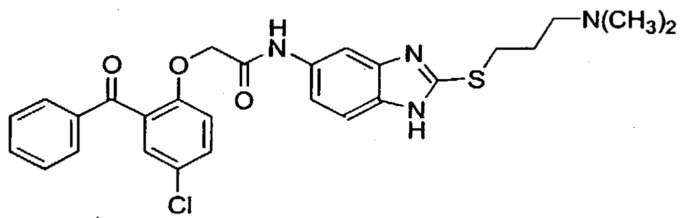
159

Ester **158**, water, and ethanol (150 mL) were used according to general procedure III, except that sodium hydroxide (5 mL of a 5N aqueous solution) was used in place of lithium hydroxide. The solvents were removed under reduced pressure to afford **159** as white crystals (5.4 g, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85 (d, 1H), 6.05 (d, 1H), 7.89 (m, 8H).

Step C:

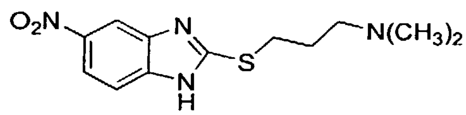
Carboxylic acid **159**, amine **140**, EDAC, HOBt and DMF were used according to general procedure IV to afford **157** as a yellow foam (0.28 g, 17%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.92 (m, 4H), 2.08 (ddd, 2H), 2.22 (s, 3H), 2.62-2.85 (m, 6H), 4.03 (t, 2H), 5.96 (d, 1H), 6.16 (d, 1H), 6.73 (br s, 2H), 7.30-7.85 (m, 7H), 7.85 (m, 7H), 8.2 (s, 1H).

__Example 71__:



160

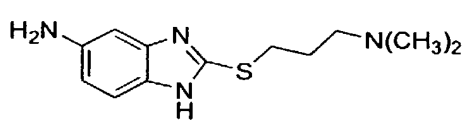
Step A:



161

Into a round-bottom flask were placed 2-mercapto-5-nitrobenzimidazole (2.0 g, 10.2 mmol), K_2CO_3 (2.8 g, 20.4 mmol) and 3-(N,N-dimethylamino)-1-chloropropane hydrochloride (1.6 g, 10.2 mmol) and DMF (50 mL). The resulting mixture was allowed to stir at rt for 24 h, after which time the DMF was removed under reduced pressure to afford a brown oil. The product was purified by flash chromatography using 9:1 dichloromethane/methanol as eluant to afford **161** (1.5 g, 54%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.12 (ddd, 2H), 2.24 (s, 6H), 3.68 (t, 2H), 3.28 (t, 2H), 5.28 (s, 1H), 7.24 (dd, 1H), 8.18 (dd, 1H), 8.28 (s, 1H).

Step B:



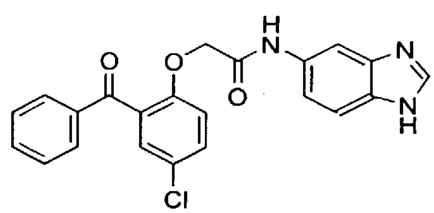
162

Into a stirred Parr bottle were placed compound **161** (1.50 g, 5.36 mmol), Pd/C (0.15 g, 10% w/w), and ethanol (300 mL). The bottle was pressurized to 5 atm. with hydrogen gas and the mixture was allowed to stir at rt for 3 h. The mixture was then filtered through a pad of celite and the solvents were removed under reduced pressure to afford **162** as an orange oil (0.80 g, 58%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91 (ddd, 2H), 2.27 (s, 6H), 3.18 (t, 2H), 3.47 (br s, 2H), 3.68 (br s, 2H), 6.54 (dd, 1H), 6.71 (s, 1H), 7.26 (dd, 1H), 8.27 (s, 1H).

Step C:

Carboxylic acid **105**, amine **162**, EDAC, HOBt, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol as eluant to afford **160** as white crystals (0.24 g, 14%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (ddd, 2H), 2.48 (s, 6H), 2.96 (t, 2H), 3.20 (br s, 2H), 4.62 (s, 2H), 5.22 (s, 1H), 6.86-8.20 (m, 11H), 9.00 (s, 1H).

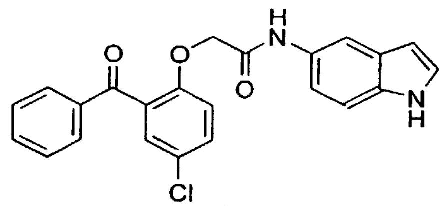
Example 72:



163

Carboxylic acid **105**, 5-aminobenzimidazole, HOBt, EDAC and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **163** as white crystals (0.28 g, 35%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.66 (s, 2H), 6.97-8.16 (m, 11H), 9.11 (s, 1H), 10.1 (br s, 1H).

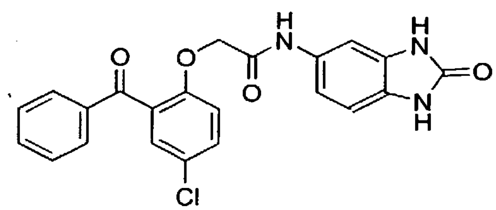
Example 73:



164

Carboxylic acid **105**, 5-aminoindole, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **164** as white crystals (0.25 g, 32%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.71 (s, 2H), 6.58 (s, 1H), 7.06-8.72 (m, 14H).

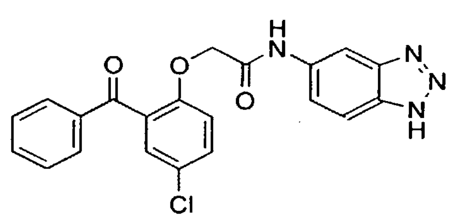
Example 74:



165

Carboxylic acid **105**, 5-aminobenzimidazolone, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **165** as white crystals (0.44 g, 27%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.71 (s, 2H), 6.83-7.86 (m, 11H), 9.62 (s, 1H), 10.55 (s, 1H), 10.59 (s, 1H).

Example 75:

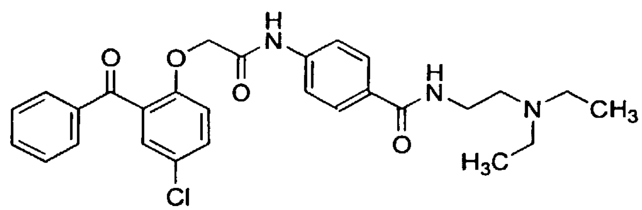


166

Carboxylic acid **105**, 5-aminobenztriazole, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5

dichloromethane/methanol to afford **166** as white crystals (0.75 g, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.79 (s, 2H), 7.06-8.61 (m, 11H), 9.81 (s, 1H), 12.60 (br s, 1H).

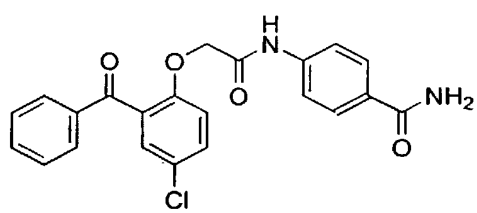
<u>Example 76:</u>



167

Carboxylic acid **105**, N1-[2-(diethylamino)ethyl]-4-aminobenzamide, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **167** as white crystals (0.12 g, 12%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, 6H), 2.83 (q, 4H), 2.90 (dd, 2H), 3.66 (dd, 2H), 4.73 (s, 2H), 7.04-7.95 (m, 13H), 9.43 (s, 1H).

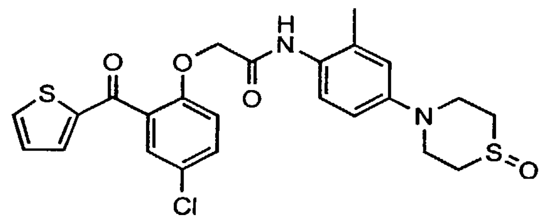
<u>Example 77</u>



168

Carboxylic acid **105**, 4-aminobenzamide, HOBt, EDAC, and DMF were used according to general procedure IV. The product was purified by flash chromatography using 95:5 dichloromethane/methanol to afford **168** as white crystals (0.13 g, 13%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.75 (s, 2H), 5.34 (s, 2H), 7.06-7.97 (m, 12H), 9.53 (s, 1H).

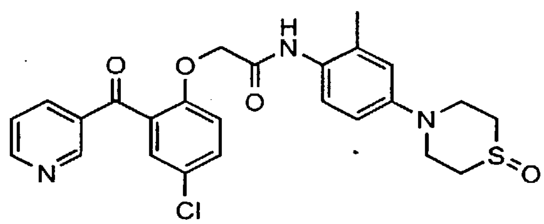
<u>Example 78:</u>



169

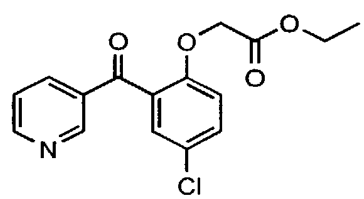
Carboxylic acid **112** (0.15 g, 0.51 mmol), amine **399** (0.11 g, 0.51 mmol), HOBt (0.7 g, 0.51 mmol), EDAC (0.98 g, 0.51 mmol), Et_3N (0.14 mL, 0.10 g, 1.0 mmol) and anhydrous DMF (7 mL) were used according to general procedure IV. Treatment of the resulting yellow oil with diethyl ether provided **169** (0.052 g, 20 %) as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.08 (d, J= 4.8 Hz, 1H), 7.63 (d, J= 3.2 Hz, 1H), 7.58 (d, J= 9.2 Hz, 1H), 7.50 (s, 1H), 7.20 (m, 3H), 6.84 (s, 1H), 6.78 (d, J= 8 Hz, 1H), 4.75 (s, 2H), 3.70 (m, 2H), 3.54 (m, 2H), 2.87 (m, 2H), 2.64 (m, 2H), 2.02 (s, 3H).

Example 79:



170

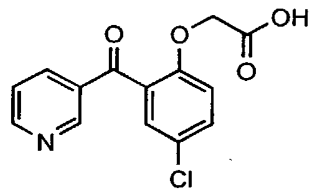
Step A:



171

Phenol **21** (1.5 g, 6.4 mmol), K_2CO_3 (4.4 g, 32.2 mmol), ethyl bromoacetate (0.79 mL, 1.18 g, 7.1 mmol) and acetone (150 mL) were used according to general procedure II to provide **171** as an oil (4.0 g, >100%). The product was used in the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, J= 1.6 Hz, 1H), 8.75 (d, J= 4 Hz, 1H), 8.18 (d, J= 7.6 Hz, 1H), 7.43 (m, 3H), 6.78 (d, J= 8.8 Hz, 1H), 4.50 (s, 2H), 4.17 (m, 2H), 1.20 (m, 3H).

Step B:



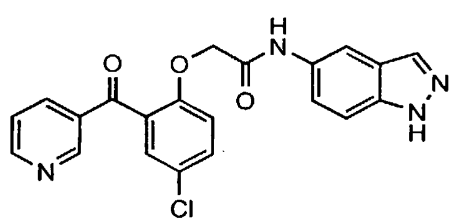
172

Ester **171** (4.0 g, 12.5 mmol), THF (25 mL), water (12 mL), EtOH (12 mL) and LiOH (1.32 g, 31.5 mmol) were used according to general procedure III. Treatment of the resulting yellow gel with ether provided **172** (1.09 g, 29%) as a pale yellow solid. The product was used in the next reaction without any further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, J= 2 Hz, 1H), 8.75 (d, J= 4.8 Hz, 1H), 8.10 (d, J= 8 Hz, 1H), 7.56 (m, 2H), 7.47 (d, J= 2.8 Hz, 1H), 7.10 (d, J= 8.8 Hz, 1H), 4.82 (s, 2H).

Step C:

Carboxylic acid **172** (0.10 g, 0.34 mmol), amine **399** (0.076 g, 0.34 mmol), HOBt (0.046 g, 0.34 mmol), EDAC (0.19 g, 0.34 mmol), Et_3N (0.1 mL, 0.68 mmol) and anhydrous DMF (5 mL) were used according to general procedure IV. Treatment of resulting oil with diethyl ether provided **170** (0.036 g, 21 %) as a pale yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.88 (s, 1H), 8.75 (s, 1H), 8.10 (d, J= 7.6 Hz, 1H), 7.63 (d, J= 8.8 Hz, 1H), 7.49 (m, 2H), 7.20 (d, J= 8.8 Hz, 1H), 7.05 (d, J= 8.8 Hz, 1H), 6.81 (s, 1H), 6.75 (d, J= 8.8 Hz, 1H), 4.67 (s, 2H), 3.69 (m, 2H), 3.51 (m, 2H), 2.86 (m, 2H), 2.63 (m, 2H), 1.96 (s, 3H).

Example 80:

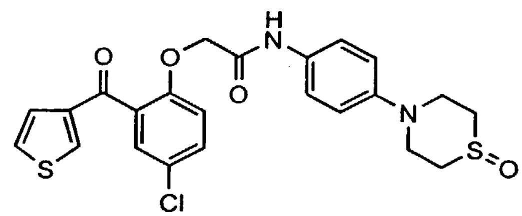


173

Carboxylic acid **172** (0.10 g, 0.34 mmol), 5-aminoindazole (0.045 g, 0.34 mmol), HOBt (0.046 g, 0.34 mmol), EDAC (0.19 g, 0.34 mmol), Et_3N (0.1 mL, 0.68 mmol) and anhydrous DMF (5 mL) were used according to general procedure IV. Treatment of

resulting oil with diethyl ether provided **173** (0.067 g, 49%) as a brown solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 9.82 (s, 1H), 8.91 (d, J= 2 Hz, 1H), 8.71 (m, 1H), 8.14 (d, J= 8 Hz, 1H), 7.99 (s, 2H), 7.61 (dd, J= 2.4, 8.8 Hz, 1H), 7.50 (m, 2H), 7.44 (d, J= 8.8 Hz, 1H), 7.29 (d, J= 9 Hz, 1H), 7.19 (d, J= 9 Hz, 1H), 4.70 (s, 2H). MS (ES): 407 (M^+).

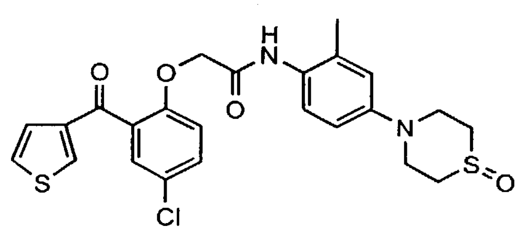
Example 81:



174

Carboxylic acid **119** (0.15 g, 0.51 mmol), amine **399** (0.11 g, 0.51 mmol), HOBt (0.07 g, 0.51 mmol), EDAC (0.1 g, 0.51 mmol), Et_3N (0.14 mL, 0.10 g, 1.0 mmol) and anhydrous DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 2% MeOH:CH_2Cl_2 as eluant to provide a yellow oil. Treatment of the oil with diethyl ether provided **174** (0.065 g, 26%) as a pale yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.26 (s, 1H), 7.62 (m, 1H), 7.58 (m, 2H), 7.45 (m, 3H), 7.16 (d, J= 9 Hz, 1H), 6.93 (m, 2H), 4.70 (s, 2H), 3.66 (m, 2H), 3.50 (m, 2H), 2.87 (m, 2H), 2.66 (m, 2H). MS (ES): 489 (M^+).

Example 82:

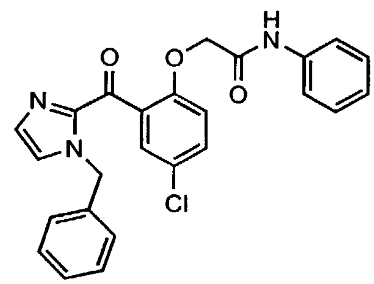


175

Carboxylic acid **119** (0.15 g, 0.51 mmol), amine **399** (0.11 g, 0.51 mmol), HOBt (0.07 g, 0.51 mmol), EDAC (0.1 g, 0.51 mmol), Et_3N (0.14 mL, 0.10 g, 1.0 mmol) and anhydrous DMF (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 2% MeOH:CH_2Cl_2 as eluant to provide a yellow oil. Treatment of the oil with diethyl ether provided **175** (0.046 g, 18%) as a pale yellow solid:

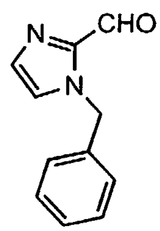
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.24 (s, 1H), 7.58 (m, 2H), 7.49 (s, 1H), 7.42 (s, 1H), 7.18 (m, 2H), 6.78 (m, 2H), 4.73 (s, 2H), 3.69 (m, 2H), 3.54 (m, 2H), 2.87 (m, 2H), 2.65 (m, 2H), 2.01 (s, 3H). MS (ES): 503 (M^+).

Example 83:



176

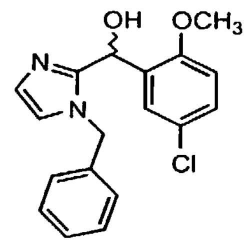
Step A:



177

In a round bottom flask equipped with a stir bar, an addition funnel and nitrogen on demand, were placed 1-benzylimidazole (2.0 g, 12.6 mmol) and anhydrous THF (50 mL) and cooled to –78 °C by means of a dry ice/ acetone bath. n-Butyllitium (8.8 mL of a 1.6 M soln. in hexanes, 13.7 mmol) was added dropwise and the reaction was allowed to stir for 15-20 min at –78 °C. Anhydrous N,N-dimethylformamide (1.3 mL, 0.0013 mmol) was added dropwise and reaction was allowed to stir for an additional 45 min at –78 °C. When judged to be complete, the reaction was quenched by dropwise addition of water and extracted with EtOAc. The organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide **177** (2.1 g, 88 %) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 7.73 (s, 1H), 7.30 (m, 4H), 7.16 (d, J= 7 Hz, 2H), 5.57 (s, 2H).

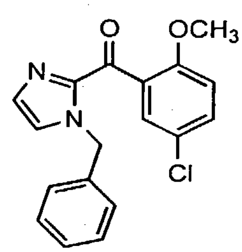
Step B:



178

In a round bottom flask equipped with a stir bar, an addition funnel and nitrogen on demand, were placed 2-bromo-4-chloroanisole (1.5 mL, 2.4 g, 11.4 mmol) and diethyl ether (17 mL) and cooled to –78 °C by means of a dry ice/ acetone bath. n-Butyllithium (7.8 mL of a 1.6 M soln. in hexanes, 12.5 mmol) was added in a dropwise manner via addition funnel and the reaction was allowed to stir for 30 min at –78 °C, after which time the reaction was quenched by dropwise addition of water and extracted with EtOAc. The organics were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide **178** (1.5 g, 42 %) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 4H), 7.16 (m, 1H), 7.00 (m, 3H), 6.83 (d, J= 2.4 Hz, 1H), 6.71 (dd, J= 3, 9 Hz, 1H), 6.11 (d, J= 2.4 Hz, 1H), 5.07 (m, 2H), 4.49 (bs, 1H), 3.73 (s, 3H).

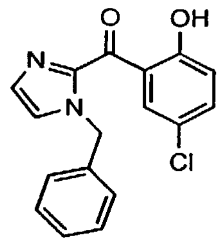
Step C:



179

In a round bottom flask equipped with a stir bar and nitrogen on demand was placed alcohol **178** (1.5 g, 4.6 mmol), CH_2Cl_2 (55 mL) and MnO_2 (4.0 g, 46 mmol). The reaction was allowed to stir at RT for 30 min, after which time, the reaction was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to provide **179** (1.5 g, >99 %) as a clear gel: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J= 4 Hz, 1H), 7.37 (m, 4H), 7.32 (m, 3H), 7.11 (s, 1H), 6.91 (d, J= 12 Hz, 1H), 5.71 (s, 2H), 3.75 (s, 3H).

Step D:



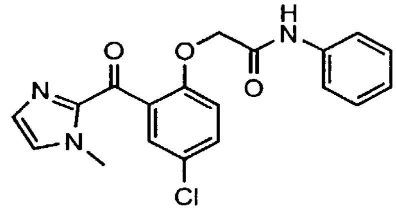
180

Anisole **179** (1.5 g, 4.6 mmol), CH_2Cl_2 (30 mL) and BBr_3 (12 mL of a 1.0 M soln. in CH_2Cl_2, 11.5 mmol) were used according to general procedure IX. The resulting brown oil was filtered through a pad of silica gel using CH_2Cl_2 as eluant and the solvents were removed under reduced pressure to provide **180** (0.9 g, 64%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.34 (m, 9H), 6.96 (d, J= 9 Hz, 1H), 5.65 (s, 2H).

Step E:

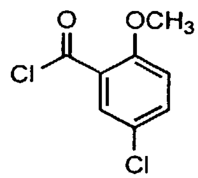
In a round bottom flask equipped with a stir bar, reflux condenser and nitrogen on demand were added the phenol **180** (0.1 g, 0.32 mmol), acetone (7 mL), K_2CO_3 (0.22 g, 1.6 mmol) and 2'-chloroacetanilide (0.058 g, 0.34 mmol). The reaction was allowed to stir at reflux for 18-24 h, after which it was poured into a separatory funnel containing water and ethyl acetate. The organics were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting product was purified by flash chromatography using 3:1 hexanes/ethyl acetate to 1:3 hexanes/ethyl acetate as a solvent gradient to provide **176** (0.077 g, 54 %) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.70 (m, 3H), 7.39 (m, 11H), 6.94 (d, J= 9 Hz, 1H), 5.79 (s, 2H), 4.71 (s, 2H). MS(ES): 445(M^+), 446 $(M+H)^+$.

__**Example 84:**__



181

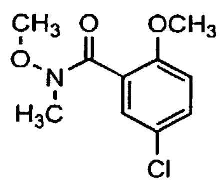
Step A:



182

5-Chloro-*o*-anisic acid (7.5 g, 40.2 mmol), CH_2Cl_2 (75 mL), oxalyl chloride (3.7 mL, 5.3 g, 42.2 mmol), and N,N-dimethylformamide (4-5 drops) were used according to general procedure V to afford **182** (8.0 g, 97%) as a yellow oil. The product was used in the next step without further purification or characterization.

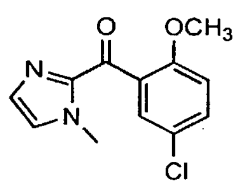
Step B:



183

Acid chloride **182** (8.0 g, 39 mmol), N,O-dimethylhydroxylamine hydrochloride (7.6 g, 78.0 mmol), $CHCl_3$ (100 mL), and triethylamine (27 mL, 19.7 g, 195 mmol) were used according to general procedure VII. The resulting colorless oil was treated with diethyl ether to provide **183** (6.0 g, 67 %) as a white solid. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (d, J= 8.4 Hz, 1H), 7.27 (d, J= 2.4 Hz, 1H), 3.75 (s, 3H), 3.42 (bs, 3H), 3.19 (bs, 3H). MS (ES): 229(M^+).

Step C:

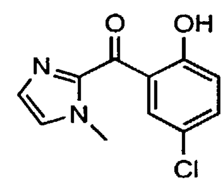


184

In a round bottom flask equipped with a stir bar , an addition funnel and nitrogen on demand, 1-methylimidazole (2.0 g, 24.4 mmol) was dissolved in diethyl ether (50 mL) and cooled to –78 °C by means of a dry ice/ acetone bath. N-Butyllithium (15 mL of a 1.6 M soln. in hexanes, 24.4 mmol) was added dropwise and the reaction was allowed to stir for 30 min at –78 °C. Amide **183** (5.1 g, 22.2 mmol) was added as a solid maintaining

reaction temp at –78 °C. When judged to be complete, the reaction was quenched by dropwise addition of water and extracted with EtOAc. The organics were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting product was purified by flash chromatography using 1:1 hexanes/ethyl acetate to provide **184** (3.3 g, 55 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.53 (dd, J= 3, 9 Hz, 1H), 7.42 (d, J= 3 Hz, 1H), 7.17 (m, 1H), 7.13 (s, 1H), 4.03 (s, 3H), 3.73 (s, 3H).

Step D:



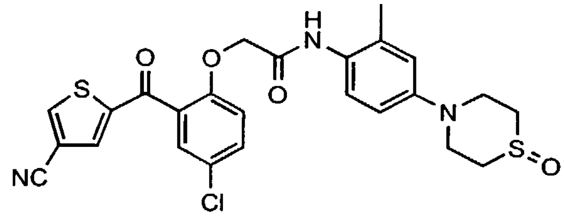
185

Anisole **184** (3.3 g, 13.2 mmol), CH_2Cl_2 (60 mL), and BBr_3 (53 mL of a 1.0 M soln. in CH_2Cl_2, 53 mmol) were used according to general procedure IX to provide **185** (2.0 g, 69%) as a yellow solid. The product was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.83 (d, J= 2 Hz, 1H), 7.62 (s, 1H), 7.56 (dd, J= 3, 9 Hz, 1H), 7.04 (d, J= 9 Hz, 1H), 4.03 (s, 3H).

Step E:

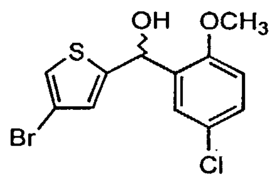
In a round bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand were added the phenol **185** (0.15 g, 0.67 mmol), acetone (5 mL), K_2CO_3 (0.46 g, 3.3 mmol), and the amide **142** (0.12 g, 0.70 mmol). The reaction was allowed to stir at reflux for 18-24 h, after which time the reaction was poured into a separatory funnel containing water and ethyl acetate. The organics were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash chromatography using 3:1 hexanes/EtOAc to 1:3 hexanes/EtOAc as a solvent gradient to provide **181** (0.065 g, 25 %) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 7.55 (m, 5H), 7.29 (t, J= 8 Hz, 2H), 7.10 (m, 3H), 4.74 (s, 2H), 4.02 (s, 3H).

<u>Example 85:</u>



186

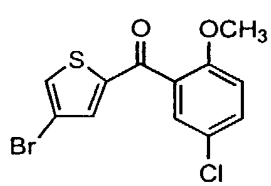
Step A:



187

In a round bottom flask equipped with a stir bar, an addition funnel and nitrogen on demand was added 2-bromo-4-chloroanisole (9.8 mL, 15.7 g, 71.3 mmol) and anhydrous THF (120 mL) and the reaction was cooled to –78 °C by means of a dry ice/ acetone bath. N-Butyllitium (45 mL of a 1.6 M soln. in hexanes, 72 mmol) was added dropwise and the reaction was allowed to stir for 30 min at –78 °C. 4-Bromo-2-thiophenecarboxaldehyde (15 g, 79 mmol) was added and the reaction temperature was maintained at –78 °C. When judged to be complete, the reaction was quenched by dropwise addition of water and extracted with ethyl acetate. The organics were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide **187** (16.3 g, 62%). The product was used in the next step without further purification or characterization.

Step B:

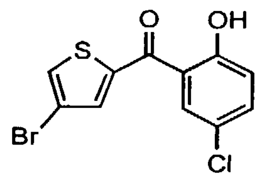


188

In a round bottom flask equipped with a stir bar and nitrogen on demand were placed the alcohol **187** (16.3 g, 49 mmol), CH_2Cl_2 (200 mL), and MnO_2 (21.1 g, 240 mmol). The reaction was allowed to stir at RT for 18-24h, after which time the mixture was filtered through a pad of celite and the solvents were removed under reduced pressure to provide **188** (2.3 g, 14 %) as an orange oil. The product was used in the next step without further

purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.55 (m, 1H), 7.45 (m, 2H), 7.19 (d, J= 9 Hz, 1H), 3.72 (s, 3H).

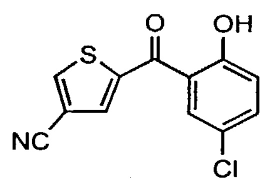
Step C:



189

Anisole **188** (2.3 g, 7.0 mmol), CH_2Cl_2 (100 mL), and BBr_3 (21 mL of a 1.0 M soln. in CH_2Cl_2, 21 mmol) were used according to general procedure to provide **189** (2.1 g, 94%) as a yellow solid. The product was used without further purification in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.24 (s, 1H), 7.57 (d, J= 1.2 Hz, 1H), 7.46 (m, 2H), 7.02 (d, J= 9 Hz, 1H).

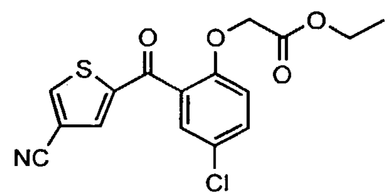
Step D:



190

In a round bottom flask equipped with a stir bar and nitrogen on demand was added the phenol **189** (2.1 g, 6.6 mmol), N-methylpyrollidinone (100 mL), and CuCN (1.2 g, 13.2 mmol) and the reaction was heated to reflux for 2-5h. When judged to be complete, the reaction was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, treated with activated carbon, dried over Na_2SO_4, filtered through a pad of celite and the solvents were removed under reduced pressure. The resulting brown oil was purified by flash chromatography using 5% MeOH/CH_2Cl_2 as eluant to provide **190** (0.5 g, 29 %) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 8.26 (s, 1H), 7.85 (s, 1H), 7.79 (s, 1H), 7.51 (d, J= 9 Hz, 1H), 7.05 (d, J= 9 Hz, 1H).

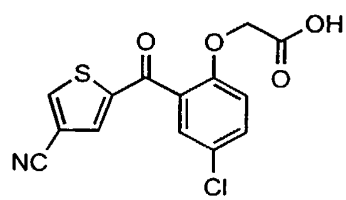
Step E:



191

Phenol **190** (0.5 g, 1.9 mmol), K_2CO_3 (0.66 g, 4.7 mmol), ethyl bromoacetate (0.2 mL, 0.32 g, 1.9 mmol) and acetone (20 mL) were used according to general procedure II to provide **191** as a clear oil (0.7 g, >100%). The product was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.09 (s, 1H), 7.62 (dd, J= 3, 9 Hz, 1H), 7.54 (d, J= 3 Hz, 1H), 7.17 (d, J= 9 Hz, 1H), 4.81 (s, 2H), 4.07 (m, 2H), 1.21 (m, 3H).

Step F:



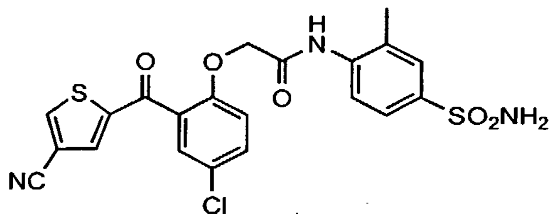
192

Ester **191** (0.7 g, 2 mmol), THF (10 mL), water (5 mL), EtOH (5 mL) and LiOH (0.2 g, 5 mmol) were used according to general procedure III to provide **192** (0.5 g, 80 %) as an orange gel. The product was used in the next step without further purification or characterization.

Step G:

Carboxylic acid **192** (0.16 g, 0.49 mmol), amine **399** (0.13 g, 0.34 mmol), HOBt (0.079 g, 0.34 mmol), EDAC (0.14 g, 0.34 mmol) and anhydrous DMF (7 mL) were used according to general procedure IV. Treatment of resulting product with diethyl ether provided **186** (0.052 g, 21 %) as a pale yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.94 (s, 1H), 8.12 (s, 1H), 7.62 (d, J= 9 Hz, 1H), 7.53 (d, J= 2.4 Hz, 1H), 7.20 (d, J= 9 Hz, 1H), 7.14 (d, J= 9 Hz, 1H), 6.84 (s, 1H), 6.77 (d, J= 8 Hz, 1H), 4.77 (s, 2H), 3.70 (m, 2H), 3.52 (m, 2H), 2.87 (m, 2H), 2.63 (m, 2H), 2.03 (s, 3H). MS(ES): 528 (M^+).

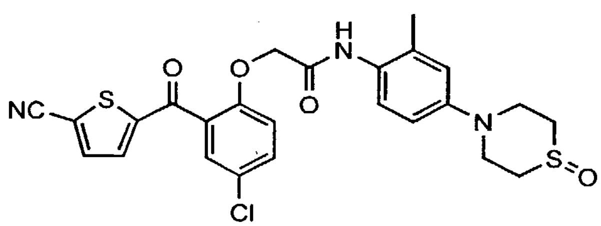
Example 86:



193

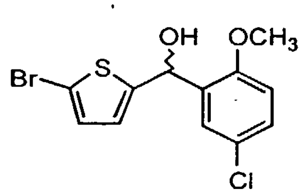
In a round bottom flask equipped with a stir bar and nitrogen on demand was added the acid **192** (0.36 g, 1.1 mmol), CH_2Cl_2 (20 mL) and oxalyl chloride (0.1 mL, 0.14 g, 1.1 mmol). The mixture was cooled to 0 °C and N,N-dimethylformamide (1-2 drops) was added. The reaction was allowed to warm to rt over a period of 30-60 min, after which time the mixture was concentrated under reduced pressure to afford the acid chloride. The acid chloride, acetonitrile (20 mL), triethylamine (0.4 mL, 0.29 g, 2.9 mmol) and the sulfonamide (0.26 g, 1.4 mmol) were combined and allowed to stir at RT for 18-24 h. When judged to be complete, the reaction was poured into a separatory funnel containing water and ethyl acetate. The organics were collected, dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure. The resulting gel was treated with diethyl ether to provide **193** (0.11 g, 20%) as a pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.95 (s, 1H), 8.11 (s, 1H), 7.61 (m, 6H), 7.23 (s, 2H), 4.87 (s, 2H), 2.23 (s, 3H).

Example 87:



194

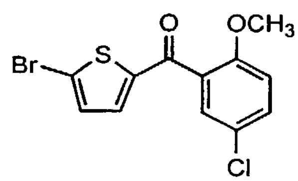
Step A:



195

In a round bottom flask equipped with a stir bar, an addition funnel and nitrogen on demand was added 2-bromo-4-chloroanisole (9.8 mL, 15.7 g, 71.3 mmol) and diethyl ether (250 mL). The reaction was cooled to –78 °C by means of a dry ice/acetone bath, and n-butyllitium (45 mL of a 1.6 M soln. in hexanes, 72 mmol) was added dropwise, the reaction was allowed to stir for 30 min at –78 °C, after which 5-bromo-2-thiophenecarboxaldehyde (15 g, 79 mmol) was added. When judged to be complete, the reaction was quenched by dropwise addition of water and extracted with ethyl acetate. The organics were collected, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide **195** (20 g, 77%). The product was used in the next step without further purification or characterization.

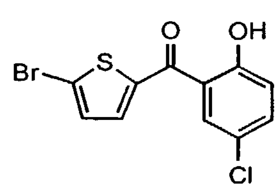
Step B:



196

To a round bottom flask equipped with a stir bar and nitrogen on demand was added the alcohol **195** (20 g, 60 mmol), CH_2Cl_2 (300 mL), and MnO_2 (15.6 g, 180 mmol). The reaction was allowed to stir at RT for 90 min, after which time it was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to provide **196** (15.3 g, 77 %) as a pale yellow oil. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (m, 1H), 7.42 (s, 1H), 7.33 (t, J= 3, 9 Hz, 1H), 7.26 (t, J= 3 Hz, 1H), 7.17 (m, 1H), 3.72 (s, 3H).

Step C:

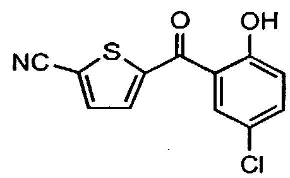


197

Anisole **196** (8.2 g, 25 mmol), CH_2Cl_2 (175 mL), and BBr_3 (74 mL of a 1.0 M soln. in CH_2Cl_2, 74 mmol) were used according to general procedure IX to provide **197** (6.8 g, 87%). The product was used in the next step without further purification. ^{1}H NMR (400

MHz, DMSO-d_6) δ 10.35 (s, 1H), 7.39 (dd, J= 2.4, 6 Hz, 1H), 7.35 (m, 4H), 6.94 (dd, J= 3, 9 Hz, 1H).

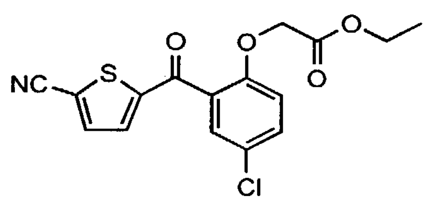
Step D:



198

In a round bottom flask equipped with a stir bar and nitrogen on demand was added the phenol **197** (8.5 g, 27 mmol), N-methylpyrrolidinone (350 mL), and copper (I) cyanide (4.8 g, 54 mmol) and the reaction mixture was heated to reflux for 2-5h. When judged to be complete, the reaction was allowed to cool to rt and poured into a beaker containing ethyl acetate and water. The organics were collected, treated with activated carbon, dried over Na_2SO_4, filtered through a pad of celite and the solvents were removed under reduced pressure. The resulting brown oil was purified by flash chromatography using 5% $MeOH/CH_2Cl_2$ as eluant to provide **198** (6.8 g, 21 %) as a yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.57 (s, 1H), 8.04 (t, J= 2 Hz, 1H), 7.68 (m, 1H), 7.48 (m, 2H), 7.03 (d, J =8.4 Hz, 1H). MS (ES): 262 $(M-H)^-$.

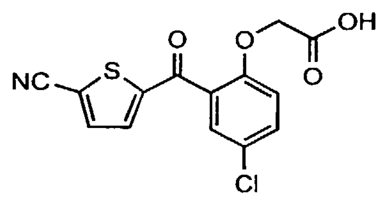
Step E:



199

Phenol **198** (1.5 g, 5.7 mmol), K_2CO_3 (3.9 g, 29 mmol), ethyl bromoacetate (0.7 mL, 1.1 g, 6.3 mmol) and acetone (125 mL) were used according to general procedure II to provide **199** as a clear oil (2.0 g, >100%). The product was used in the next step without further purification or characterization.

Step F:



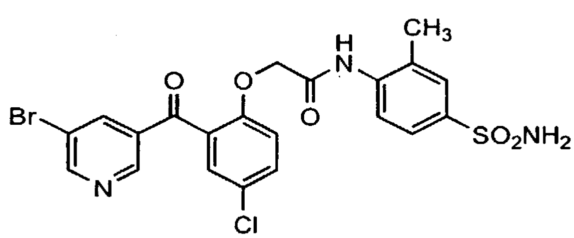
200

Ester **199** (2.0 g, 5.7 mmol), THF (20 mL), water (10 mL), EtOH (10 mL) and LiOH (1.0 g, 22.8 mmol) were used according to general procedure III to provide **200**(0.42 g, 23 %) as an orange gel. The product was used in the next step without further purification or characterization.

Step G:

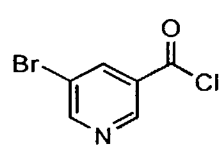
Carboxylic acid **200** (0.42 g, 1.3 mmol), amine **399** (0.36 g, 1.6 mmol), HOBt (0.22 g, 1.6 mmol), EDAC (0.38 g, 2.0 mmol) and anhydrous DMF (7 mL) were used according to general procedure IV. The resulting brown oil was purified by flash chromatography using 2 % MeOH/CH_2Cl_2 as eluant. Treatment of the resulting product with diethyl ether provided **194** (0.071 g, 10 %) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.08 (s, 1H), 7.83 (d, J= 4.5 Hz, 1H), 7.69 (m, 2H), 7.61 (s, 1H), 7.27 (d, J= 9 Hz, 1H), 7.18 (d, J= 9 Hz, 1H), 6.90 (s, 1H), 6.83 (d, J= 8.4 Hz, 1H), 4.80 (s, 2H), 3.76 (m, 2H), 3.58 (m, 2H), 2.93 (m, 2H), 2.71 (m, 2H), 2.07 (s, 3 H).

<u>**Example 88:**</u>



201

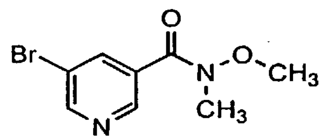
Step A:



202

5-Bromonicotinic acid (5.0g, 0.025 mol), oxalyl chloride (2.4 mL, 3.5g, 0.027 mol), methylene chloride (125 mL), and N,N-dimethylformamide (2 drops) were used according to general procedure V to provide **202** (6.0g, >100%) as a white solid. The product was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.04 (d, J= 1.5 Hz, 1H), 8.97 (d, J= 2.1 Hz, 1H), 8.44 (t, J= 1.8 Hz, 1H).

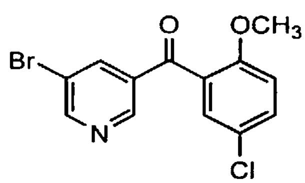
Step B:



203

Acid chloride **202** (4.0 g, 0.018 mol), N,O-dimethylhydroxylamine hydrochloride (3.5 g, 0.036 mol), Et_3N (7.5 mL, 5.5 g, 0.054 mol), and $CHCl_3$ (150 mL) were used according to general procedure VII to provide **203** (3.2 g, 74%) as a yellow oil. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J= 2 Hz, 1H), 8.72 (d, J= 1.6 Hz, 1H), 8.20 (t, J= 2 Hz, 1H), 3.53 (s, 3H), 3.25 (s, 3H).

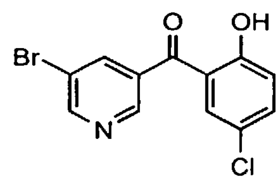
Step C:



204

Amide **203** (1.8 g, 7.3 mmol), n-butyllithium (5.0 mL of a 1.6 M soln. in hexanes, 8.0 mmol), 2-bromo-4-chloroanisole (1.0 mL, 1.6 g, 7.3 mmol), and diethyl ether (20 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 7:3 hexanes:ethyl acetate as eluant to afford **204** (1.5 g, 63%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, J= 2.4 Hz, 1H), 8.71 (d, J= 2 Hz, 1H), 8.21 (t, J= 2 Hz, 1H), 7.63 (dd, J=2.8, 9.2 Hz, 1H), 7.48 (d, J=2.8 Hz, 1H), 7.22 (d, J=9.2 Hz, 1H), 3.65 (s, 3H).

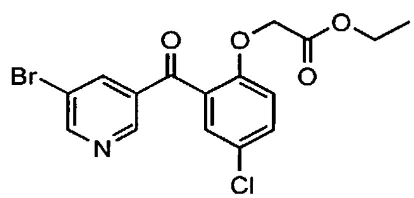
Step D:



205

Anisole **204** (2.0 g, 6.1 mmol), BBr_3 (18.4 mL of a 1.0 M soln. in CH_2Cl_2, 18.4 mmol), and CH_2Cl_2 (50 mL) were used according to general procedure IX to afford **205** (3.4 g, >100%) as a yellow foam. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 8.91 (d, J= 2.4 Hz, 1H), 8.75 (d, J= 1.6 Hz, 1H), 8.21 (t, J=2 Hz, 1H), 7.48 (dd, J=2.8, 8.8 Hz, 1H), 7.41 (d, J=2.8 Hz, 1H), 6.97 (d, J=8.8 Hz, 1H). MS (ES): 314 $(M+H)^+$, 312 $(M-H)^-$.

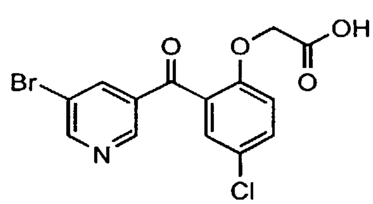
Step E:



206

Phenol **205** (0.55 g, 1.7 mmol), ethyl bromoacetate (0.21 mL, 0.32 g, 1.9 mmol), K_2CO_3 (0.73 g, 5.3 mmol), and acetone (25 mL) were used according to general procedure II to provide **206** (0.58 g, 83%) as a red oil. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (d, J= 2.4 Hz, 1H), 8.84 (d, J= 1.8 Hz, 1H), 8.30 (t, J= 1.8 Hz, 1H), 7.66 (dd, J=2.7, 9 Hz, 1H), 7.57 (d, J=2.7 Hz, 1H), 7.19 (d, J= 9 Hz, 1H), 4.82 (s, 2H), 4.18 (m, 2H), 1.2 (m, 3H).

Step F:



207

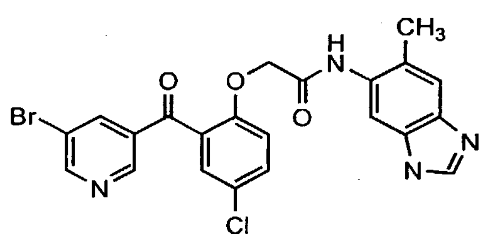
Ester **206** (0.58 g, 1.45 mmol), LiOH (0.15 g, 3.64 mmol) and a solution of THF, EtOH, and water (20 mL) were used according to general procedure III. The resulting orange

residue was treated with diethyl ether to afford **207** (0.2 g, 42%) as a yellow solid. The product was used the next step without further purification or characterization.

Step G:

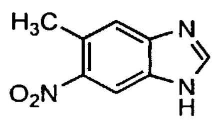
Acid **207** (91 mg, 0.25 mmol), oxalyl chloride (0.023 mL, 33 mg, 0.26 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (42 mg, 0.23 mmol), $NaHCO_3$ (105 mg, 1.25 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The resulting yellow residue was washed with several portions of diethyl ether to afford **201** (20 mg, 15%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.89 (d, J= 2.4 Hz, 1H), 8.83 (d, J= 1.6 Hz, 1H), 8.29 (t, J=2 Hz, 1H), 7.65 (dd, J=2.8, 8.8 Hz, 1H), 7.62 (s, 1H), 7.58 (m, 2H), 7.53 (d, J=2.8 Hz, 1H), 7.22 (m, 3H), 4.79 (s, 2H), 2.15 (s, 3H). MS (ES): 538 $(M-H)^-$.

<u>**Example 89:**</u>



208

Step A:

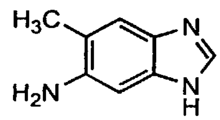


209

To a round-bottom flask equipped with a stir bar was added 5-methylbenzimidazole (4.0 g, 0.030 mol), and concentrated H_2SO_4 (65 mL). The reaction was cooled to 0 °C and potassium nitrate (2.75 g, 0.027 mol) was added portion-wise. After stirring for 1 h, the reaction was poured over ice and solid Na_2CO_3 was added to adjust to pH >8. The aqueous layer was extracted with ethyl acetate, the organics were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford a yellow solid. The solid was

recrystallized using 1:1 methanol:water, making sure to filter any undissolved material while mixture was hot, to obtain **209** (1.8 g, 34 %) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.96 (bs, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.65 (s, 1H), 2.64 (s, 3H). MS (ES): 222 $(M-H)^-$.

Step B:



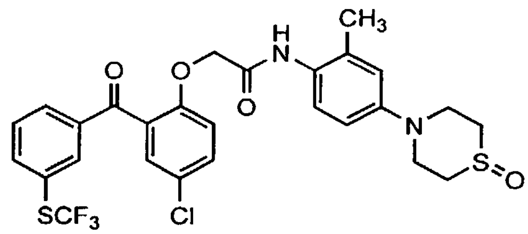
210

To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **209** (2.2 g, 0.012 mol), absolute ethanol (75 mL), and palladium on charcoal (0.23 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 psig for 16 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide a residue. The residue was washed several times with diethyl ether to afford **210** (1.0g, 57%) as a pink solid. At ambient temperature, the product exists as a mixture of tautomers. ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 11.60 (bs, 1H), 7.79 (s, 1H), 7.20 (s, 1H), 6.82 (s, 1H), 4.39 (bs, 2H), 2.20 (s, 3H). MS (ES): 148 $(M+H)^+$.

Step C:

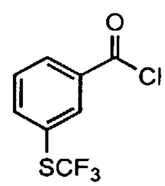
Acid **207** (0.1 g, 0.27 mmol), HOBt (40 mg, 0.27mmol), EDAC (52 mg, 0.27 mmol), , aniline **210** (40 mg, 0.27 mmol), and N,N-dimethylformamide (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 2% MeOH: 1% Et_3N: $CHCl_3$ as eluant to afford **208** (7.6 mg, 5%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.85 (m, 2H), 8.30 (s, 1H), 8.12 (s, 1H), 7.66 (d, J= 7 Hz, 1H), 7.53 (m, 2H), 7.37 (m, 1H), 7.23 (d, J= 9 Hz, 1H), 4.75 (s, 2H), 2.12 (s, 3H). MS (ES): 501 $(M+H)^+$.

<u>**Example 90:**</u>



211

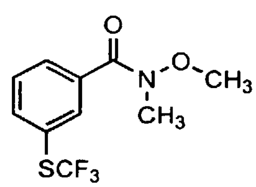
Step A:



212

3-(Trifluoromethylthio)benzoic acid (2.0g, 9.0 mmol), oxalyl chloride (0.8 mL, 1.14 g, 9.0 mmol), methylene chloride (50 mL), and N,N-dimethylformamide (4 drops) were used according to general procedure V to provide **212** (2.0 g, 94%). The product was used in the next step without further purification or characterization.

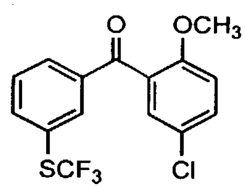
Step B:



213

Acid chloride **212** (2.0 g, 8.3 mmol), N,O-dimethylhydroxylamine hydrochloride (2.0 g, 20.5 mmol), Et_3N (2.4 mL, 1.7 g, 16.8 mmol), and $CHCl_3$ (40 mL) were used according to general procedure VII to provide **213** (1.6 g, 70%) as a clear oil. The product was used in the next step without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.79 (m, 2H), 7.60 (t, 1H), 3.50 (s, 3H), 3.24 (s, 3H).

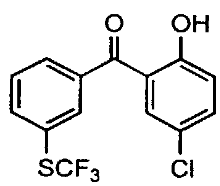
Step C:



214

Amide **213** (0.8 g, 3.0 mmol), n-butyllithium (1.3 mL of a 2.5 M soln. in hexanes, 3.3 mmol), 2-bromo-4-chloroanisole (0.41 mL, 0.66 g, 3.0 mmol), and diethyl ether (10 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 7:3 hexanes:ethyl acetate as eluant to afford **214** (0.56 g, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J= 8 Hz, 1H), 7.87 (m, 2H), 7.68 (d, J= 8 Hz, 1H), 7.60 (dd, J= 2.4, 8.8 Hz, 1H), 7.45 (d, J=2.8 Hz, 1H), 7.21 (d, J= 8.8 Hz, 1H), 3.62 (s, 3H).

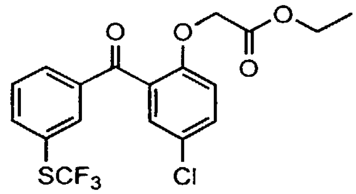
Step D:



215

Anisole **214** (0.56 g, 1.6 mmol), BBr_3 (2.0 mL of a 1.0 M soln. in CH_2Cl_2, 2.0 mmol), and CH_2Cl_2 (10 mL) were used according to general procedure IX to afford **215** (0.45 g, 86%). The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 7.95 (m, 2H), 7.87 (d, J= 8 Hz, 1H), 7.66 (t, J=8 Hz, 1H), 7.44 (dd, J=2.8, 8.8 Hz, 1H), 7.35 (d, J=2.8 Hz, 1H), 6.96 (d, J=8.8 Hz, 1H). MS (ES): 331 (M-H)$^-$

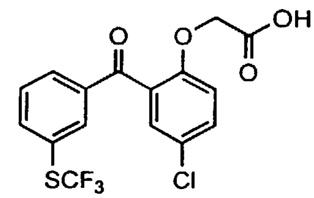
Step E:



216

Phenol **215** (0.45 g, 1.4 mmol), ethyl bromoacetate (0.17 mL, 0.25 g, 1.5 mmol), K_2CO_3 (0.48 g, 2.5 mmol), and acetone (20 mL) were used according to general procedure II to provide **216** (0.6 g, >100%) as a yellow oil. The product was used in the next step without further purification or characterization.

Step F:



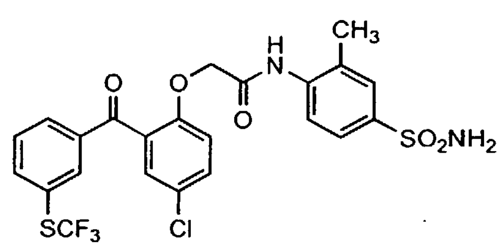
217

Ester **216** (0.6 g, 1.4 mmol), LiOH (0.15 g, 3.64 mmol) and a solution of THF, EtOH, and water (15 mL) were used according to general procedure III. The resulting yellow oil was treated with hexanes to afford **217** (0.2 g, 36%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J= 7.6 Hz, 1H), 8.06 (s, 1H), 7.92 (d, J= 7.2 Hz, 1H), 7.60 (t, J= 7.6 Hz, 1H), 7.46 (dd, J= 2.8, 9.2 Hz, 1H), 7.33 (d, J=2.4 Hz, 1H), 6.85 (d, J= 9.2 Hz, 1H), 3.96 (s, 2H). MS (ES): 389 $(M-H)^-$.

Step G:

Acid **217** (50 mg, 0.13 mmol), HOBt (18 mg, 0.13mmol), EDAC (25 mg, 0.13 mmol), aniline **399** (29 mg, 0.13 mmol), and N, N-dimethylformamide (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ as eluant and treated with several portions of hexanes to afford **211** (40 mg, 51%) as a beige solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.00 (s, 1H), 7.96 (d, J= 1.6 Hz, 1H), 7.94 (d, J= 1.2 Hz, 1H), 7.64 (m, 2H), 7.49 (d, J=2.4 Hz, 1H), 7.20 (d, J=8.8 Hz, 1H), 7.06 (d, J= 8.8 Hz, 1H), 6.81 (d, J= 2.8 Hz, 1H), 6.75 (dd, J= 2.4, 8.8 Hz, 1H), 4.65 (s, 2H), 3.69 (m, 2H), 3.51 (m, 2H), 2.86 (m, 2H), 2.64 (m, 2H), 1.96 (s, 3H). MS (ES): 597 (M^+), 596 $(M-H)^-$.

<u>**Example 91**</u>

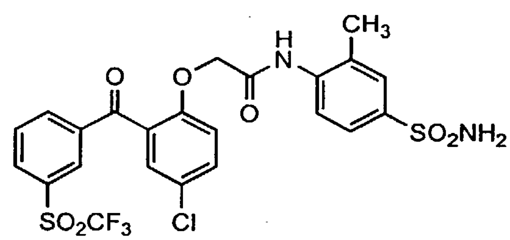


218

Acid **217** (70 mg, 0.18 mmol), oxalyl chloride (0.017 mL, 25 mg, 0.20 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general

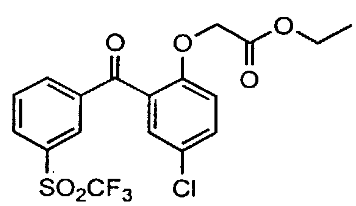
procedure V to afford the acid chloride. The acid chloride, aniline **466** (39 mg, 0.21 mmol), $NaHCO_3$ (84 mg, 1.0 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The resulting yellow solid was washed with minimal diethyl ether to afford **218** (50 mg, 45%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 9.44 (s, 1H), 8.38 (m, 3H), 8.01 (m, 1H), 7.70 (m, 5H), 7.31 (m, 3H), 4.80 (s, 2H), 2.16 (s, 3H). MS (ES): 559 (M^+).

Example 92



219

Step A:

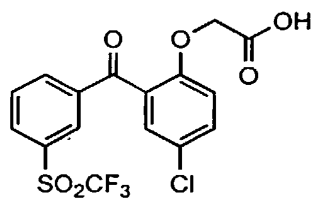


220

To a round-bottom flask equipped with a stir bar, nitrogen on demand, and an addition funnel, were placed the ester **216** (0.56 g, 1.34 mmol) and CH_2Cl_2 (25 mL) and the reaction mixture was cooled to 0 °C. A solution of m-chloroperoxybenzoic acid in CH_2Cl_2 (10 mL) was added dropwise via addition funnel and the resulting mixture was allowed to stir at 0 °C for 0.5 h, after which time it was allowed to warm to rt and stir for an additional 16 h. When judged to be complete, the reaction was quenched with 10% sodium metabisulfite solution and extracted with CH_2Cl_2. The organics were collected, washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford **220** (0.56 g, 93%) as a pale yellow oil. The product was used in the next reaction without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J= 8 Hz, 1H), 8.29 (d, J= 8 Hz, 1H), 8.22 (s, 1H), 7.96 (t, J= 7.6 Hz, 1H), 7.62

(dd, J= 2.8, 9.2 Hz, 1H), 7.55 (d, J=2.8 Hz, 1H), 7.17 (d, J=8.8 Hz, 1H), 4.70 (s, 2H), 4.05 (m, 2H), 1.21 (m, 3H).

Step B:



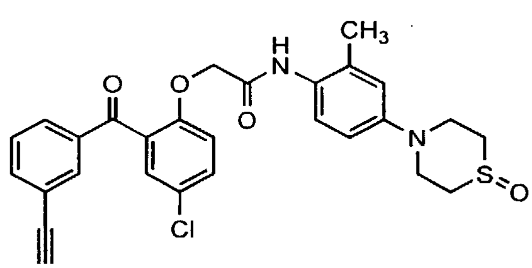
221

Ester **220** (0.56 g, 1.2 mmol), LiOH (0.13g, 3.1 mmol) and a solution of THF, EtOH, and water (15 mL) were used according to general procedure III to afford **221** (0.1 g, 19%). The product was used in the next step without further purification or characterization.

Step C:

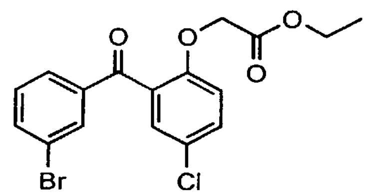
Acid **221** (100 mg, 0.24 mmol), oxalyl chloride (0.023 mL, 33 mg, 0.26 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (41 mg, 0.22 mmol), $NaHCO_3$ (100 mg, 1.2 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ to afford **219** (72 mg, 51%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.01 (s, 1H), 7.96 (m, 2H), 7.61 (m, 6H), 7.49 (s, 1H), 7.23 (m, 2H), 4.76 (s, 2H), 2.12 (s, 3H).

__Example 93__



222

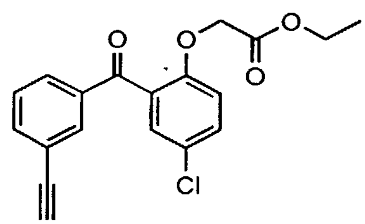
Step A:



223

Phenol **432** (10 g, 0.032 mol), ethyl bromoacetate (3.5 mL, 5.3 g, 0.032 mol), K_2CO_3 (11 g, 0.080 mol), and acetone (120 mL) were used according to general procedure II to afford **223** (11.5 g, 91%) as a yellow oil. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (m, 2H), 7.68 (d, J= 7.6 Hz, 1H), 7.53 (dd, J= 2.4, 8.8 Hz, 1H), 7.44 (m, 2H), 7.09 (d, J= 9.2 Hz, 1H), 4.74 (s, 2H), 4.04 (q, J= 7.2 Hz, 2H), 1.13 (m, 3H).

Step B:

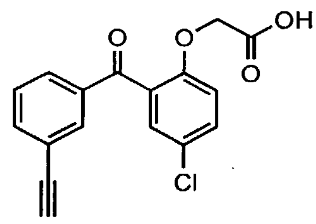


224

To a round-bottom flask equipped with a stir bar and nitrogen on demand were added the ester **223** (1.5 g, 3.8 mmol), trimethylsilylacetylene (0.6 mL, 0.4 g, 4.1 mmol), tetrakis(triphenylphosphine)palladium (0) (0.31 g, 0.27 mmol), copper(I) iodide (0.15 g, 0.80 mmol), triethylamine (1.7 mL, 1.2 g, 0.80 mmol), and N,N-dimethylformamide (15 mL) and the reaction was allowed to stir at 80 °C for 18h. When judged to be complete, the reaction mixture was poured into ethyl acetate and water. The organics were collected, washed with water and brine, dried over Na_2SO_4, filtered through a pad of celite, and the solvents were removed under reduced pressure. To the resulting residue was added tetrahydrofuran (20 mL) and tetrabutylammonium fluoride (3 mL). The mixture was allowed to stir at RT for 10 min, after which it was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The resulting product was purified by flash chromatography using 7:3 hexanes:ethyl acetate to provide **224** (0.69 g, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (m, 2H), 7.54 (m, 2H), 7.44 (s, 1H), 7.34

(m, 1H), 7.09 (d, J= 9.2 Hz, 1H), 4.74 (s, 2H), 4.04 (m, 2H), 1.11 (m, 3H). MS (ES): 343 (M^+).

Step C:



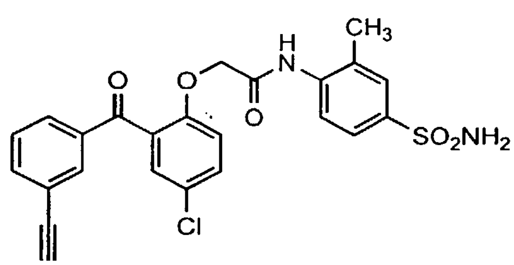
225

Ester **224** (0.69 g, 2.0 mmol), LiOH (0.2 g, 5.0 mmol) and a solution of THF, EtOH, and water (12 mL) were used according to general procedure III to afford **225** (0.37 g, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (bs, 1H), 7.86 (s, 1H), 7.73 (m, 2H), 7.54 (m, 2H), 4.62 (s, 2H), 4.25 (s, 1H).

Step D:

Acid **225** (75 mg, 0.24 mmol), HOBt (32 mg, 0.24mmol), EDAC (46 mg, 0.24 mmol), aniline **399** (53 mg, 0.24 mmol), and N, N-dimethylformamide (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ as eluant and treated with several portions of hexanes to afford **222** (17 mg, 14%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 7.75 (m, 2H), 7.70 (d, J= 7.6 Hz, 1H), 7.60 (dd, J= 2.8, 9.2 Hz, 1H), 7.49 (t, J= 8 Hz, 1H), 7.45 (d, J= 2.8 Hz, 1H), 7.21 (d, J= 9.2 Hz, 1H), 7.09 (d, J= 8.8 Hz, 1H), 6.81 (s, 1H), 6.75 (m, 1H), 4.66 (s, 2H), 4.28 (s, 1H), 3.69 (m, 2H), 3.52 (m, 2H), 2.86 (m, 2H), 2.63 (m, 2H), 1.96 (s, 3H). MS (ES): 521 (M^+).

<u>**Example 94**</u>

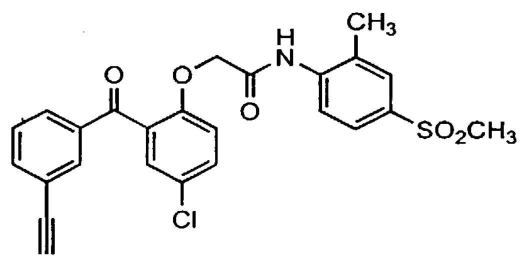


226

Step A:

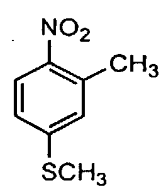
Acid **225** (80 mg, 0.25 mmol), oxalyl chloride (0.024mL, 35mg, 0.28 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (3 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (48 mg, 0.26 mmol), $NaHCO_3$ (105 mg, 1.3 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ to afford **226** (20 mg,16%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.77 (d, J= 7.6 Hz, 1H), 7.70 (d, J= 7.6 Hz, 1H), 7.58 (m, 4H), 7.45 (m, 2H), 7.22 (m, 3H), 4.77 (s, 2H), 4.27 (s, 1H), 2.13 (s, 3H). MS ES): 482 (M^+), 481 $(M-H)^-$.

<u>**Example 95**</u>



227

Step A:

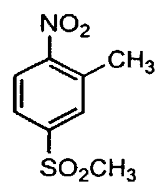


228

To a round-bottom flask equipped with a stir bar and nitrogen on demand was added 5-fluoro-2-nitrotoluene (2.4 mL, 3.0 g, 0.019 mol), sodium thiomethoxide (1.5 g, 0.021 mol), and N,N-dimethylformamide (50 mL). The reaction was allowed to stir at 85 °C for 2-4 h, after which time the reaction mixture was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, washed with water, dried over Na_2SO_4, treated with activated carbon, filtered through celite and the solvents were removed under reduced pressure to afford **228** (2.95 g, 85%) as an orange oil. The product

was used in the next step without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.29 (d, J= 1.6 Hz, 1H), 7.24 (dd, J= 2, 8.4 Hz, 1H), 2.52 (s, 3H), 2.50 (s, 3H).

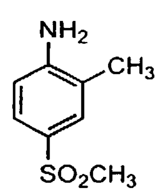
Step B:



229

To a round-bottom flask equipped with a stir bar and nitrogen on demand was added **228** (2.95 g, 0.016 mol) and CH_2Cl_2 (50 mL). The reaction was cooled to 0°C and a solution of m-chloroperoxybenzoic acid (5.8 g, 0.033 mol) in CH_2Cl_2 (10 mL) was added dropwise via addition funnel. The resulting mixture was allowed to stir at 0 °C for 0.5 h, after which time it was allowed to warm to RT and stir for an additional 3-4h. When judged to be complete, the reaction was quenched with 10% sodium metabisulfite solution and extracted with CH_2Cl_2. The organics were collected, washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford **229** (3.0 g, 88%) as yellow solid. The product was used in the next reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J= 8.4 Hz, 1H), 7.92 (m, 2H), 3.08 (s, 3H), 2.65 (s, 3H).

Step C:



230

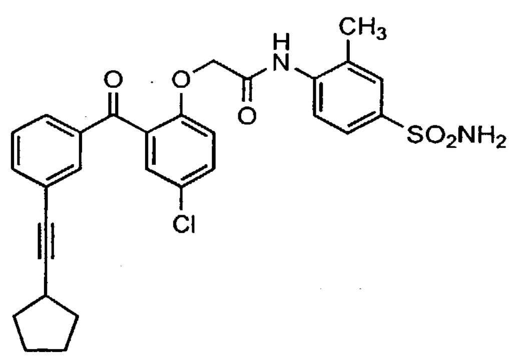
To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **229** (1.5 g, 6.9 mmol), toluene (50 mL), and palladium on charcoal (0.15 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 p.s.i. for 7 h. When judged to be complete, the reaction was filtered through a celite plug and the

solvents were removed under reduced pressure to provide a crystalline material. The residue was washed several times with diethyl ether to afford **230** (1.3 g, >99%). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.36 (m, 2H), 6.65 (d, J= 8.4 Hz, 1H), 5.81 (s, 2H), 2.98 (s, 3H), 2.06 (s, 3H).

Step D:

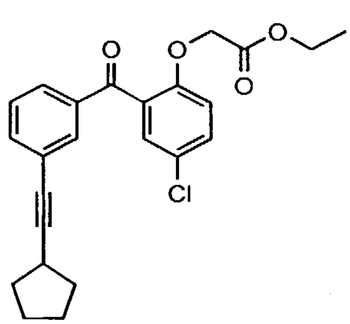
Acid **225** (107 mg, 0.34 mmol), oxalyl chloride (0.032mL, 47mg, 0.37 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **230** (63 mg, 0.34 mmol), $NaHCO_3$ (143 mg, 1.7 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ to afford **227** (8 mg, 5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.34 (s, 1H), 7.73 (m, 6H), 7.60 (dd, J= 2.8, 8.8 Hz, 1H), 7.50 (t, J= 8 Hz, 1H), 7.46 (d, J= 2.4 Hz, 1H), 7.21 (d, J= 8.8 Hz, 1H), 4.79 (s, 2H), 4.29 (s, 1H), 3.27 (s, 3H), 2.18 (s, 3H). MS ES): 481 (M-H)$^-$.

__Example 96__



231

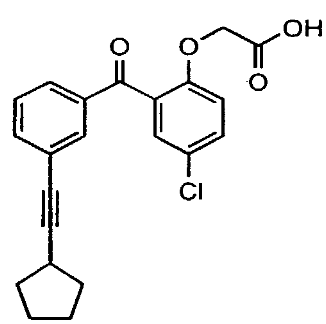
Step A:



232

To a round-bottom flask equipped with a stir bar and nitrogen on demand were added the ester **223** (0.2 g, 0.5 mmol), cyclopentylacetylene (52 mg, 0.55 mmol), tetrakis(triphenylphosphine)palladium (0) (40 mg, 0.035 mmol), copper(I) iodide (20 mg, 0.11 mmol), triethylamine (0.22 mL, 0.16 g, 1.6 mmol), and N,N-dimethylformamide (5 mL) and the reaction was allowed to stir at 80 °C for 18h. When judged to be complete, the reaction mixture was poured into ethyl acetate and water. The organics were collected, washed with water, dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 8:2 hexanes: ethyl acetate to afford **232** (130 mg, 63%) as an orange oil. ^{1}H NMR (300 MHz, DMSO-d-$_6$) δ 7.68 (m, 3H), 7.59 (dd, J= 2.7,9 Hz, 1H), 7.48 (m, 2H), 7.13 (d, J= 9 Hz, 1H), 4.79 (s, 2H), 4.10 (m, 2H), 2.88 (m, 1H), 2.00 (m, 2H), 1.63 (m, 6H), 1.17 (m, 3H).

Step B:



233

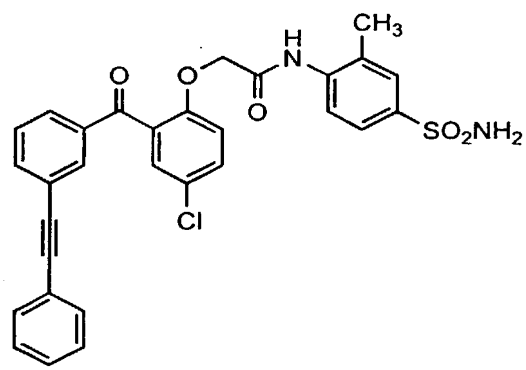
Ester **232** (0.13 g, 0.32 mmol), LiOH (33 mg, 0.79 mmol) and a solution of THF, EtOH, and water (8 mL) were used according to general procedure III to afford **233** (0.15 g, >99%). The product was used in the next step without further purification or characterization.

Step C:

Acid **233** (140 mg, 0.37 mmol), oxalyl chloride (0.033mL, 48mg, 0.38 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (5 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (73 mg, 0.39 mmol), $NaHCO_3$ (155 mg, 1.85 mmol), acetone (7 mL), and water (0.5 mL) were used

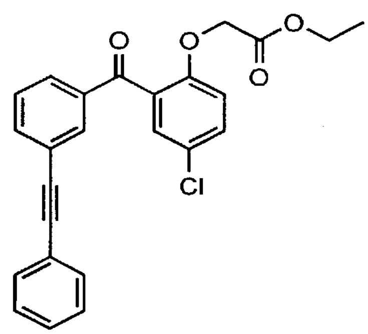
according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ to afford **231** (88 mg, 43%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.61 (m, 8H), 7.44 (m, 2H), 7.21 (m, 2H), 4.77 (s, 2H), 2.81 (m, 1H), 2.14 (s, 3H), 1.93 (m, 2H), 1.58 (m, 6H).

Example 97



234

Step A:

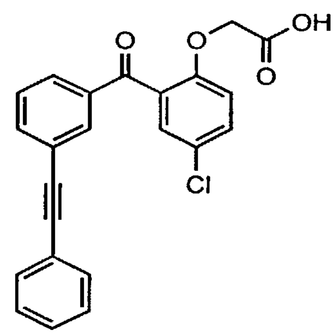


235

To a round-bottom flask equipped with a stir bar and nitrogen on demand were added the ester **223** (0.2 g, 0.5 mmol), phenylacetylene (52 mg, 0.55 mmol), tetrakis(triphenylphosphine)palladium (40 mg, 0.035 mmol), copper(I) iodide (20 mg, 0.11 mmol), triethylamine (0.22 mL, 0.16 g, 1.6 mmol), and N,N-dimethylformamide (5 mL) and the reaction was allowed to stir at 80 °C for 18 h. When judged to be complete, the reaction mixture was poured into ethyl acetate and water. The organics were collected, washed with water, dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 8:2 hexanes:ethyl acetate to afford **235** (150 mg, 72%) as a green oil. ^1H NMR (300 MHz,

DMSO-d_6) δ 7.87 (d, J= 4.8 Hz, 1H), 7.82 (m, 2H), 7.60 (m, 4H), 7.50 (d, J= 3 Hz, 1H), 7.46 (m, 3H), 7.15 (d, J= 9 Hz, 1H), 4.82 (s, 2H), 4.10 (m, 2H), 1.21 (m, 3H).

Step B:



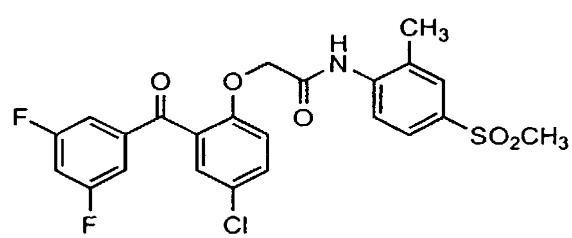
236

Ester **235** (0.15 g, 0.36 mmol), LiOH (38 mg, 0.90 mmol) and a solution of THF, EtOH, and water (8 mL) were used according to general procedure III to afford **236** (64 mg, 46%). The product was used in the next step without further purification or characterization.

Step C:

Acid **236** (64 mg, 0.16 mmol), oxalyl chloride (0.015mL, 23 mg, 0.17 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (5 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **466** (31 mg, 0.17mmol), $NaHCO_3$ (67 mg, 0.8 mmol), acetone (5 mL), and water (0.5 mL) were used according to general procedure VI. The product was filtered through a pad of silica gel to afford **234** (10 mg, 11%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 7.90 (s, 1H), 7.79 (m, 2H), 7.62 (m, 3H), 7.54 (m, 4H), 7.47 (d, J= 3 Hz, 1H), 7.38 (m, 3H), 7.22 (m, 3H), 4.80 (s, 2H), 2.15 (s, 3H).

<u>**Example 98**</u>

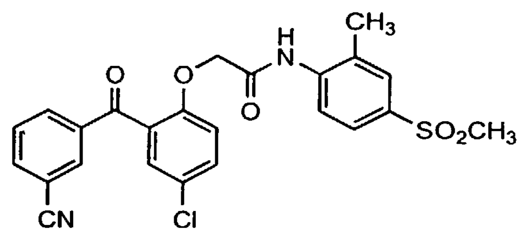


237

Step A:

Acid **49** (120 mg, 0.37 mmol), oxalyl chloride (0.035mL, 50 mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **230** (69 mg, 0.37 mmol), $NaHCO_3$ (155 mg, 1.85 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The resulting yellow oil was treated with pentanes to afford **237** (39 mg, 21%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.66 (m, 5H), 7.53 (d, J= 2.7 Hz, 1H), 7.49 (m, 2H), 7.25 (d, J= 9 Hz, 1H), 4.87 (s, 2H), 3.20 (s, 3H), 2.26 (s, 3H). MS (ES): 494 (M^+).

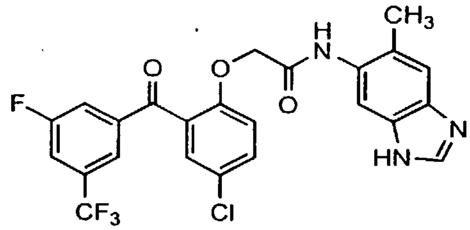
Example 99



238

Acid **129** (120 mg, 0.38 mmol), oxalyl chloride (0.037 mL, 53 mg, 0.42 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **230** (70 mg, 0.38 mmol), $NaHCO_3$ (160 mg, 1.9 mmol), acetone (7 mL), and water (0.5 mL) were used according to general procedure VI. The product purified by flash chromatography using 5% MeOH:$CHCl_3$ to afford **238** (18 mg, 10%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.16 (s, 1H), 8.06 (m, 2H), 7.67 (m, 25H), 7.49 (d, J= 2.8 Hz, 1H), 7.21 (d, J= 9.2 Hz, 1H), 4.80 (s, 2H), 3.14 (s, 3H), 2.18 (s, 3H). MS (ES): 481 $(M-H)^-$

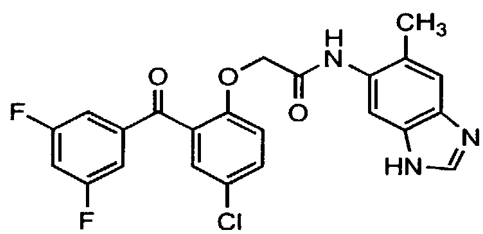
Example 100



239

Acid **71** (300 mg, 0.8 mmol), HOBt (108 mg, 0.8 mmol), EDAC (153 mg, 0.8 mmol), aniline **210** (118 mg, 0.8 mmol), and N,N-dimethylformamide (7 mL) were used according to general procedure IV. The product was purified by flash chromatography using 3% MeOH: 1% Et_3N: CH_2Cl_2 as eluant to afford **239** (60 mg, 15%) as a white solid. At ambient temp. the product exists as a mixture of tautomers. ^1H NMR (400 MHz, DMSO-d_6) δ 12.27 (m, 1H), 9.15 (m, 1H), 8.00 (s, 1H), 7.99 (d, J= 8 Hz, 1H), 7.87 (m, 2H), 7.66 (d, J= 9 Hz, 1H), 7.45 (m, 3H), 4.74 (s, 2H), 2.12 (m, 3H). MS (ES): 506 (M^+), 507 $(M+H)^+$.

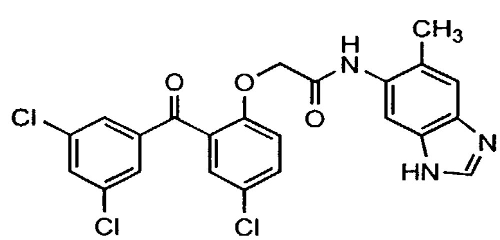
Example 101



240

Acid **49** (120 mg, 0.37 mmol), oxalyl chloride (0.035 mL, 50mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **210** (54 mg, 0.37 mmol), $NaHCO_3$ (155 mg, 1.9 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The product purified by flash chromatography using 5% MeOH:$CHCl_3$ to afford **240** (22 mg, 13%) as a pale yellow solid. At ambient temperature the product exists as a mixture of tautomers. ^1H NMR (400 MHz, DMSO-d_6) δ 12.26 (m, 1H), 9.14 (m, 1H), 8.09 (s, 1H), 7.64 (d, J= 9 Hz, 1H), 7.50 (m, 4H), 7.23 (m, 2H), 4.75 (m, 2H), 2.12 (m, 3H). MS (ES): 456 (M^+), 457 $(M+H)^+$, 455$(M-H)^-$.

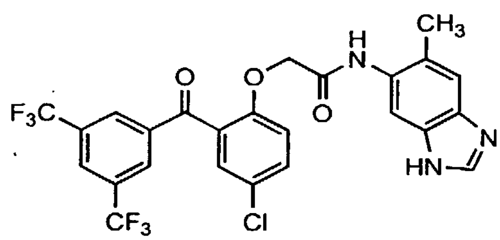
Example 102



241

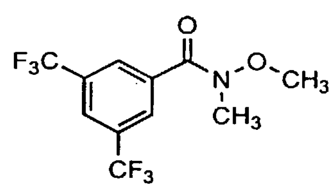
Acid **76** (120 mg, 0.33 mmol), oxalyl chloride (0.032 mL, 46 mg, 0.37 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **210** (51 mg, 0.35 mmol), $NaHCO_3$ (139 mg, 1.7 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The product purified by flash chromatography using 2% MeOH:CH_2Cl_2 to afford **241** (11 mg, 7%) as a white solid. At ambient temperature the product exists as a mixture of tautomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 9.15 (m, 1H), 8.09 (s, 1H), 7.87 (m, 1H), 7.70 (m, 2H), 7.64 (m, 1H), 7.55 (m, 2H), 7.21 (m, 1H), 4.75 (m, 2H), 2.12 (m, 3H). MS (ES): 490 $(M+H)^+$, 488 $(M-H)^-$.

Example 103



242

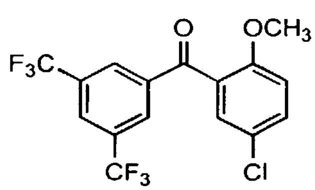
Step A:



243

3,5-Bis(trifluoromethyl)benzoyl chloride (5.0 g, 0.018 mol), N,O-dimethylhydroxylamine hydrochloride (3.5 g, 0.036 mol), Et_3N (7.5 mL, 5.5 g, 0.054 mol), and CH_2Cl_2 (50 mL) were used according to general procedure VII to provide **243** (5.0 g, 92%) as a clear oil. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.22 (s, 2H), 3.52 (s, 3H), 3.28 (s, 3H).

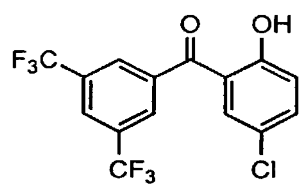
Step B:



244

Amide **243** (5.0 g, 0.017 mol), n-butyllithium (11.4 mL of a 1.6 M solution in hexanes, 0.018 mol), 2-bromo-4-chloroanisole (2.3 mL, 3.8 g, 0.017 mol), and diethyl ether (60 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 85:15 hexanes:ethyl acetate as eluant to afford **244** (3.76 g, 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.18 (s, 2H), 7.65 (t, J= 2.8 Hz, 1H), 7.52 (d, J= 2.8 Hz, 1H), 7.24 (d, J= 8.8 Hz, 1H), 3.61 (s, 3H).

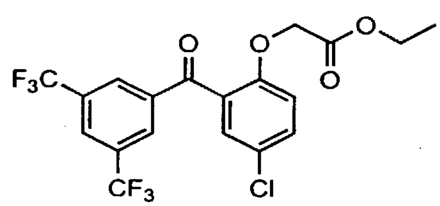
Step C:



245

Anisole **244** (3.76 g, 9.8 mmol), BBr_3 (29 mL of a 1.0 M soln. in CH_2Cl_2, 29 mmol), and CH_2Cl_2 (80 mL) were used according to general procedure IX to afford **245** (3.2 g, 89%) a pale green solid. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 1H), 8.40 (s, 1H), 8.21 (s, 2H), 7.48 (m, 2H), 6.98 (d, J= 8.8 Hz, 1H).

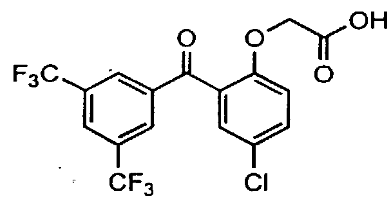
Step D:



246

Phenol **245** (3.2 g, 8.7 mmol), ethyl bromoacetate (1.1 mL, 1.6 g, 9.5 mmol), K_2CO_3 (3.0 g, 21.7 mmol), and acetone (50 mL) were used according to general procedure II to provide **246** (3.8 g, 97%) as a pale yellow solid. The product was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.31 (s, 2H), 7.68 (dd, J= 3, 9 Hz, 1H), 7.61 (d, J= 2.4 Hz, 1H), 7.21 (d, J= 9 Hz, 1H), 4.79 (s, 2H), 4.06 (q, J= 7 Hz, 2H), 1.13 (t, J= 7 Hz, 3H).

Step E:



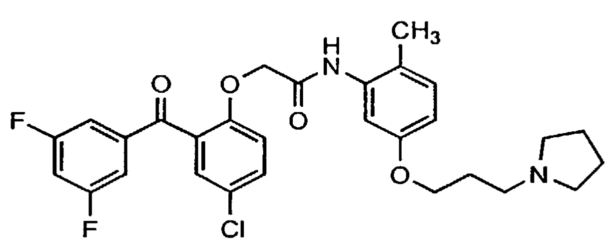
247

Ester **246** (3.8 g, 8.4 mmol), LiOH (0.88 g, 20.9 mmol) and a solution of THF, EtOH, and water (25 mL) were used according to general procedure III. The resulting white foam was treated with diethyl ether to afford **247** (3.1 g, 86%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.34 (s, 2H), 7.67 (dd, J= 3, 9 Hz, 1H), 7.58 (d, J= 3 Hz, 1H), 7.16 (d, J= 9 Hz, 1H), 4.63 (s, 2H).

Step F:

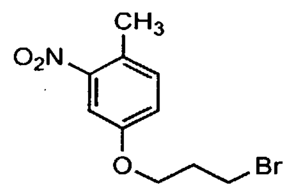
Acid **247** (150 mg, 0.35 mmol), HOBt (47 mg, 0.35 mmol), EDAC (67 mg, 0.35 mmol), aniline **210** (52 mg, 0.35 mmol), and N,N-dimethylformamide (5 mL) were used according to general procedure IV. The product was purified by flash chromatography using 3% MeOH:$CHCl_3$ as eluant to afford **242** (9 mg, 5%) as a white solid. At ambient temperature, the product exists as a mixture of tautomers. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.32 (s, 1H), 9.20 (s, 1H), 8.44 (s, 1H), 8.35 (m, 2H), 8.14 (m, 1H), 7.76 (m, 1H), 7.62 (m, 1H), 7.51 (s, 1H), 7.30 (d, J= 9 Hz, 1H), 4.77 (s, 2H), 2.13 (s, 3H). MS (ES): 556 (M^+), 557 $(M-H)^-$.

Example 104



248

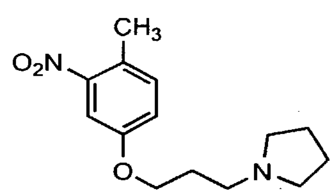
Step A:



249

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 3-methyl-4-nitrophenol (2.0 g, 0.013 mol), dibromopropane (10.6 mL, 21.0 g, 0.10 mol), potassium carbonate (2.7 g, 0.02 mol), and N, N-dimethylformamide (50 mL) and the mixture was allowed to stir at rt for 18 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing CH_2Cl_2 and water. The organics were collected, washed with 0.5 N NaOH soln., dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting red oil was distilled to afford **249** (2.46 g, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (d, J= 2.4 Hz, 1H), 7.37 (d, J= 8.4 Hz, 1H), 7.21 (dd, J= 2.4, 8.4 Hz, 1H), 4.11 (t, J= 6 Hz, 2H), 3.63 (t, J= 6 Hz, 2H), 2.38 (s, 3H), 2.22 (m, 2H).

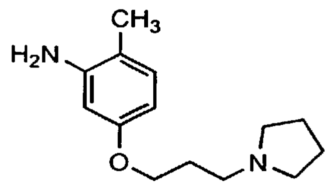
Step B:



250

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed **249** (1.5 g, 5.47 mmol), pyrrolidine (0.91 mL, 0.78 g, 10.9 mmol), potassium carbonate (1.1 g, 8.2 mmol), and N, N-dimethylformamide (30 mL) and the mixture was allowed to stir at rt for 4 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford **250** (1.24 g, 89%) as a brown oil. The product was used in the next step without further purification or characterization.

Step C:



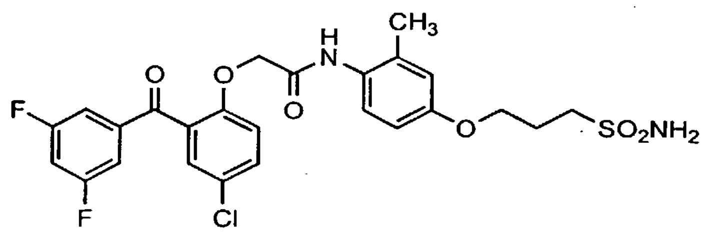
251

To a plastic-coated reaction vessel equipped with a stir bar, was added compound **250** (1.3 g, 4.9 mmol), absolute ethanol (20 mL), and palladium on charcoal (0.13 g of 10% Pd/C, 10% w/w). The vessel was placed on a hydrogenation apparatus at 60 p.s.i. for 3 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide a dark oil. The residue was treated with a small amount of ethyl acetate and hexanes and the resulting precipitate was filtered and the mother liquor was concentrated under reduced pressure to afford **251** (1.0 g, 87%), as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 (d, J= 8.4 Hz, 1H), 6.14 (d, J= 2.4 Hz, 1H), 5.98 (dd, J= 2.4, 8.4 Hz, 1H), 4.73 (s, 2H), 3.82 (t, J= 6.4 Hz, 2H), 2.46 (m, 2H), 2.37 (m, 4H), 1.92 (s, 3H), 1.77 (m, 2H), 1.63 (m, 4H).

Step D:

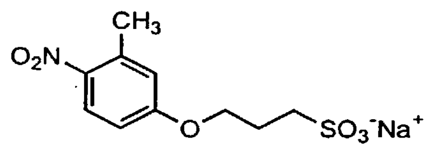
Acid **49** (120 mg, 0.37 mmol), oxalyl chloride (0.035 mL, 50 mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **251** (87 mg, 0.37 mmol), $NaHCO_3$ (155 mg, 1.85 mmol), acetone (8 mL), and water (0.5 mL) were used according to general procedure VI. The resulting yellow oil was treated with pentanes to afford **248** (92 mg, 46%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 7.62 (dd, J= 2.8, 8.8 Hz, 1H), 7.55 (t, J= 9.2 Hz, 1H), 7.47 (d, J= 2.4 Hz, 1H), 7.42 (m, 2H), 7.19 (d, J= 8.8 Hz, 1H), 7.01 (m, 2H), 6.63 (d, J= 8.4 Hz, 1H), 4.74 (s, 2H), 3.89 (t, J= 6.4 Hz, 2H), 2.45 (m, 2H), 2.39 (bs, 4H), 1.98 (s, 3H), 1.81 (t, J= 6.8 Hz, 2H), 1.63 (s, 4H). MS(ES): 543 (M^+).

<u>**Example 105**</u>



252

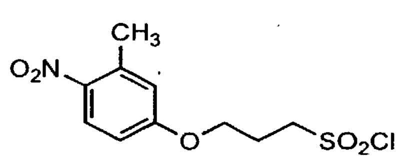
Step A:



253

To a round-bottom flask equipped with an overhead stirrer, and addition funnel, and nitrogen on demand was placed sodium hydride (7.8 g of 60% by weight in mineral oil, 0.20 mol) and anhydrous tetrahydrofuran (THF, 300 mL). The mixture was cooled to 0 °C and 2-methyl-3-nitrophenol (30 g, 0.20 mol) was added dropwise as a solution in THF (100 mL). The reaction was then allowed to warm to rt, heated to 40 °C for 15 min., and then allowed to cool to rt. At this time, 1,3-propane sultone (25.6 g, 0.21 mol) in THF (100 mL) was added dropwise and the reaction was heated to reflux for 4-6 h. When judged to be complete, the reaction mixture was filtered and the resulting solid was washed with absolute ethanol and diethyl ether and dried in a vacuum oven. A solid precipitated out of the mother liquor, was filtered and washed with absolute ethanol and diethyl ether and dried in a vacuum oven to afford **253** (27 g, 46%) of a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (d, J= 9 Hz, 1H), 7.05 (d, J= 2.7 Hz, 1H), 6.98 (dd, J= 2.7, 9.3 Hz, 1H), 4.22 (t, J= 6.6 Hz, 2H), 2.58 (m, 2H), 2.52 (s, 3H), 2.04 (m, 2H).

Step B:

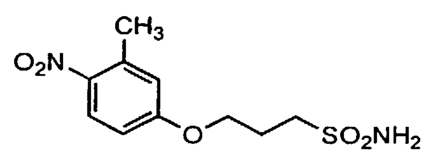


254

To a round-bottom flask equipped with a stir bar, an addition funnel, and nitrogen on demand was added the sulfonic acid salt **253** (11 g, 0.037 mol) and N,N-dimethylformamide (250 mL) and the reaction was cooled to 0 °C. Thionyl chloride (8.0

mL, 13.0 g, 0.11 mol) was added dropwise and the resulting mixture was allowed to stir at 0 °C for 0.5 h, after which time it was allowed to warm to rt and stir for an additional 3 h. When judged to be complete, the reaction mixture was poured into a beaker of ice and the resulting white precipitate was filtered and placed in a vacuum oven to afford **254** (8.7 g, 80%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (d, J= 9 Hz, 1H), 7.05 (d, J= 2.7 Hz, 1H), 6.98 (dd, J= 2.7, 9.3 Hz, 1H), 4.22 (t, J= 6.3 Hz, 2H), 2.61 (m, 2H), 2.57 (s, 3H), 2.04 (m, 2H).

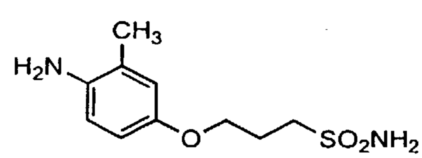
Step C:



255

To a round-bottom flask equipped with a stir bar, an addition funnel, and nitrogen on demand was added ammonium hydroxide (10 mL) and THF (20 mL) and the reaction was cooled to 0 °C. Sulfonyl chloride **254** (2 g, 6.8 mmol) was added dropwise and the reaction was allowed to stir at 0 °C for 15 min, after which time the reaction was poured into a beaker of ice and extracted with ethyl acetate. The organics were collected, washed with water, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to provide **255** (1.4 g, 77%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 (d, J= 9 Hz, 1H), 7.06 (d, J= 2.7 Hz, 1H), 7.00 (dd, J= 2.7, 9 Hz, 1H), 6.91 (s, 2H), 4.24 (t, J= 6 Hz, 2H), 3.16 (t, J= 7.5 Hz, 2H), 2.56 (s, 3H), 2.18 (m, 2H).

Step D:



256

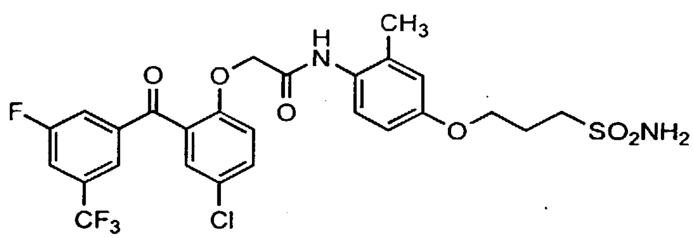
To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **255** (0.29 g, 1.1 mmol), absolute ethanol (25 mL), and palladium on charcoal (29 mg of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 60 p.s.i. for 2-4 h. When judged to be complete, the reaction was filtered through a celite

plug and the solvents were removed under reduced pressure to provide **256** (0.25 g, 98%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.80 (s, 2H), 6.54 (s, 1H), 6.49 (s, 2H), 4.34 (s, 2H), 3.89 (t, J= 6 Hz, 2H), 2.58 (m, 2H), 3.05 (m, 2H), 1.99 (m, 5H).

Step E:

Acid **49** (120 mg, 0.37 mmol), oxalyl chloride (0.035 mL, 50 mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **256** (81 mg, 0.33 mmol), $NaHCO_3$ (155 mg, 1.85 mmol), acetone (8 mL), and water (0.5 mL) were used according to general procedure VI to afford **252** (103 mg, 50%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.62 (dd, J= 2.8, 9.2 Hz, 1H), 7.55 (m, 1H), 7.47 (d, J= 2.8 Hz, 1H), 7.41 (m, 2H), 7.19 (d, J= 9.2 Hz, 1H), 7.11 (d, J= 8.4 Hz, 1H), 6.83 (s, 2H), 6.76 (d, J= 2.8 Hz, 1H), 6.69(dd, J=2.8, 8.4 Hz), 4.70 (s, 2H), 4.01 (t, J= 6.4 Hz, 2H), 3.08 (t, J= 8 Hz, 2H), 2.07 (m, 2H), 2.00 (s, 3H). MS (ES): 553 (M^+).

<u>**Example 106**</u>

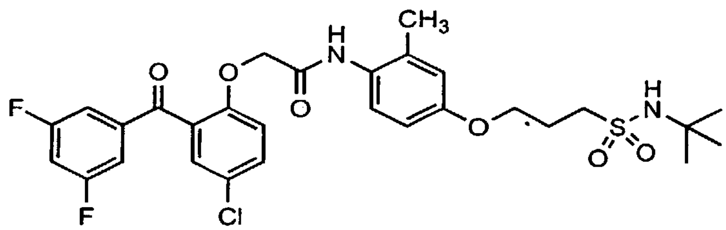


257

Acid **71** (13 g, 0.035 mol), oxalyl chloride (7.0 mL, 9.8 g, 0.077 mol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (100 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **256** (7.81 g, 0.032 mol), $NaHCO_3$ (15 g, 0.18 mol), acetone (125 mL), and water (10 mL) were used according to general procedure VI. The product was crystallized from methanol to afford **257** (10.5 g, 50%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.05 (d, J= 8.4 Hz, 1H), 7.90 (m, 2H), 7.71 (dd, J= 2.7, 9 Hz, 1H), 7.57 (d, J= 2.7 Hz, 1H), 7.25 (d, J= 9 Hz, 1H), 7.13 (d, J= 9 Hz, 1H), 6.88 (s, 2H), 6.80 (d, J= 2.7 Hz, 1H), 6.73 (dd, J= 2.7, 9 Hz, 1H), 4.74 (s, 2H), 4.07 (t, J= 6 Hz, 2H), 3.13 (m, 2H), 2.13 (m, 2H), 2.03 (s, 3H).

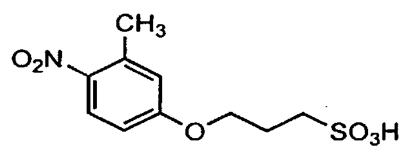
MS (ES): 602 (M-H)$^-$, 603 (M$^+$). Anal. Calcd for $C_{26}H_{23}N_2O_6ClF_4S$: C, 51.79; H, 3.84; N, 4.65. Found: C, 51.91; H, 3.88; N, 4.66.

Example 107



258

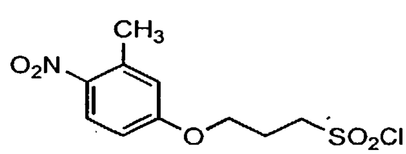
Step A:



259

To a round-bottom flask equipped with a stir bar, and nitrogen on demand were placed 2-methyl-3-nitrophenol (10 g, 0.065 mol), acetone (100 mL), potassium carbonate (27 g, 0.20 mol), and 1,3-propane sultone (6.0 mL, 8.3 g, 0.068 mol). The mixture was heated to reflux for 1 h, after which time it was allowed to cool to rt and stir for an additional 72 h. When judged to be complete, the reaction mixture was concentrated under reduced pressure. The resulting yellow residue was dissolved in a minimal amount of water, acidified to pH 2 using conc. HCl, and extracted with a mixture of absolute ethanol/ethyl acetate. The organics were collected, dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to afford **259** (10.2 g, 57%) of a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.00 (d, J= 9.2 Hz, 1H), 6.99 (d, J= 2.4 Hz, 1H), 6.92 (dd, J= 2.4, 8.8 Hz, 1H), 4.16 (t, J= 6.4 Hz, 2H), 2.47 (m, 5H), 1.98 (m, 2H).

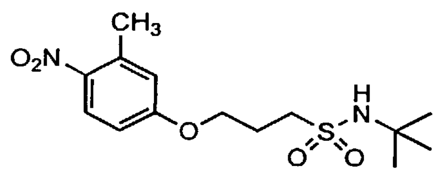
Step B:



260

To a round-bottom flask equipped with a stir bar, reflux condensor, and nitrogen on demand were added the sulfonic acid **259** (3 g, 0.011 mol) and phosphorus oxychloride ($POCl_3$, 100 mL). The reaction was heated to reflux for 18 h, after which time it continued to stir at rt for 24 h. The mixture was filtered and the $POCl_3$ was removed under reduced pressure to afford **260** (3.8 g, >100%) as a brown oil. The product was used in the next step without further purification or characterization.

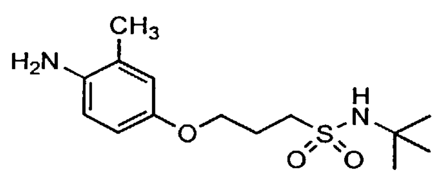
Step C:



261

To a round-bottom flask equipped with a stir bar and nitrogen on demand was added t-butylamine (0.33 mL, 0.23 g, 3.1 mmol), triethylamine (0.72 mL, 0.52 g, 5.2 mmol), and chloroform (20 mL). Sulfonyl chloride **260** (0.76 g, 2.6 mmol) in chloroform (3 mL) was added dropwise and the reaction was allowed to stir at rt for 2 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing $CHCl_3$ and water, the organics were collected, washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The resulting brown residue was filtered through a pad of silica gel, eluting with hexanes to provide **261** (0.37 g, 43%) as a white solid. The product was used in the next step without further purification or characterization.

Step D:



262

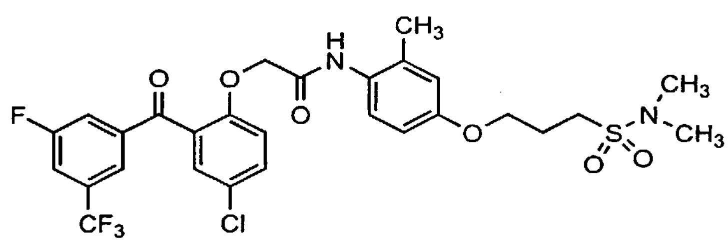
To a plastic-coated reaction vessel equipped with a stir bar, were added compound **261** (0.37 g, 1.1 mmol), ethanol (20 mL), and palladium on charcoal (37 mg of 10% Pd/C, 10w/w). The vessel was placed on a hydrogenation apparatus at 60 psig for 2-4 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide **262** (0.32 g, 95%) as brown oil. ^1H NMR

(400 MHz, DMSO-d_6) δ 6.92 (s, 1H), 6.85 (s, 1H), 6.53 (m, 1H), 6.49 (m, 1H), 4.51 (bs, 2H), 3.90 (t, J= 6 Hz, 2H), 3.09 (m, 2H), 2.08 (m, 2H), 1.99 (s, 3H), 1.22 (m, 9H).

Step E:

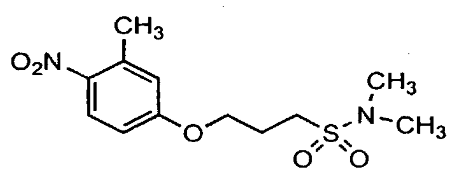
Acid **49** (120 mg, 0.37 mmol), oxalyl chloride (0.035 mL, 50 mg, 0.40 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **262** (111 mg, 0.37 mmol), $NaHCO_3$ (155 mg, 1.85 mmol), acetone (10 mL), and water (0.5 mL) were used according to general procedure VI. The product purified by flash chromatography using 5% MeOH:CH_2Cl_2 to afford **258** (28 mg, 12%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 7.63 (dd, J= 4, 8 Hz, 1H), 7.54 (m, 1H), 7.47 (d, J= 4Hz, 1H), 7.41 (m, 2H), 7.20 (d, J=8 Hz, 1H), 7.12 (d, J= 8 Hz, 1H), 6.87 (s, 1H), 6.75 (m, 1H), 6.68 (dd, J= 4, 8 Hz, 1H), 4.70 (s, 2H), 4.02 (t, J= 8 Hz, 2H), 3.09 (t, J= 8 Hz, 2H), 2.05 (t, J= 8 Hz, 2H), 2.00 (s, 3H), 1.22 (s, 9H). MS (ES): 608 $(M-H)^-$.

<u>**Example 108**</u>



263

Step A:

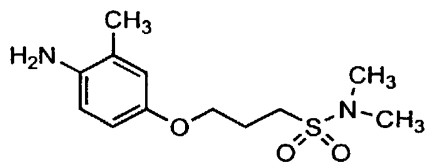


264

To a round-bottom flask equipped with a stir bar and a gas dispersion tube was added sulfonyl chloride **260** (3.8 g, 0.013 mol) and methylene chloride (100 mL), and the reaction was cooled to 0 °C. Dimethylamine gas was bubbled through the reaction mixture for 1 h, after which time the reaction mixture was poured into CH_2Cl_2 and water. The organics were collected, washed with water, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **264** (2.1 g, 54%) as a pale yellow

solid. The product was used in the next step without further purification or characterization.

Step B:



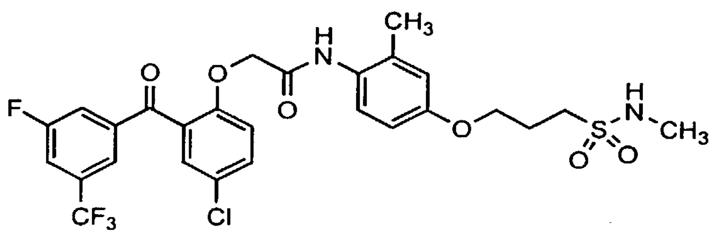
265

To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **264** (2.1 g, 7.0 mmol), absolute ethanol (40 mL), and palladium on charcoal (0.21 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 p.s.i. for 2-4 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide **265** (1.7 g, 90%) as a pale yellow solid. The product was used in the next step without further purification or characterization.

Step C:

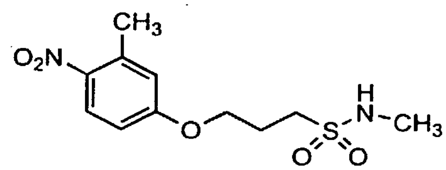
Acid **71** (120 mg, 0.32 mmol), oxalyl chloride (0.032 mL, 44 mg, 0.35 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **265** (78 mg, 0.29 mmol), $NaHCO_3$ (134 mg, 1.6 mmol), acetone (6 mL), and water (0.5 mL) were used according to general procedure VI. The resulting residue was treated several times with pentane to afford **263** (90 mg, 45%) as a beige solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.98 (d, J= 8.4 Hz, 1H), 7.84 (m, 2H), 7.65 (dd, J= 2.4, 8.8 Hz, 1H), 7.51 (d, J= 2.8 Hz, 1H), 7.20 (d, J= 8.8 Hz, 1H), 7.08 (d, J= 8.8 Hz, 1H), 6.76 (d, J= 2.4 Hz, 1H), 6.68 (dd, J= 2.8, 8.8 Hz, 1H), 4.69 (s, 2H), 4.00 (t, J= 6 Hz, 2H), 3.13 (m, 2H), 2.75 (s, 6H), 2.05 (m, 2H), 1.98 (s, 3H). MS (ES): 631 (M^+)

<u>**Example 109**</u>



266

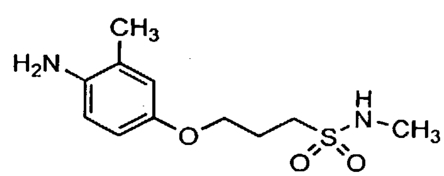
Step A:



267

To a round-bottom flask equipped with a stir bar and a gas dispersion tube was added sulfonyl chloride **260** (3.2 g, 0.011 mol) and methylene chloride (75 mL), and the reaction was cooled to 0 °C. Methylamine gas was bubbled through the reaction mixture for 1 h, after which time the reaction mixture was poured into CH_2Cl_2 and water. The organics were collected, washed with water, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was recrystallized from methanol to afford **267** (2.0 g, 63%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (d, J= 9 Hz, 1H), 7.03 (m, 3H), 4.23 (t, J= 8.4 Hz, 2H), 3.19 (m, 2H), 2.57 (m, 6H), 2.12 (m, 2H). MS (ES): 617 (M^+).

Step B:



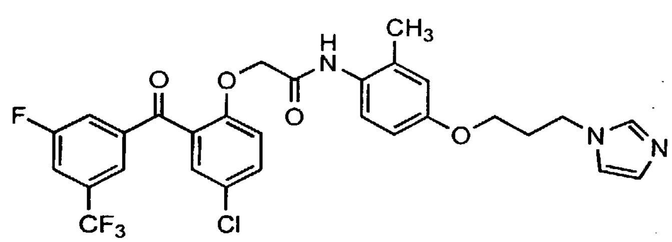
268

To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **267** (2.0 g, 6.9 mmol), toluene (25 mL), and palladium on charcoal (0.20 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 50 p.s.i. for 4 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure. The resulting residue was treated with several portions of hexanes to provide **268** (1.1 g, 62%) as a pink solid. ^{1}H NMR (400

MHz, DMSO-d_6) δ 6.92 (q, J= 5 Hz, 1H), 6.55 (s, 1H), 6.48 (m, 2H), 4.36 (bs, 2H), 3.88 (t, J= 6.4 Hz, 2H), 3.08 (m, 2H), 2.53 (d, J= 5 Hz, 3H), 1.95 (m, 5H).

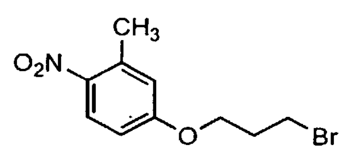
Step C:
Acid **71** (120 mg, 0.32 mmol), oxalyl chloride (0.032 mL, 44 mg, 0.35 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **268** (75 mg, 0.29 mmol), $NaHCO_3$ (134 mg, 1.6 mmol), acetone (6 mL), and water (0.5 mL) were used according to general procedure VI. The resulting residue was treated several times with hexanes to afford **266** (80 mg, 41%) as a beige solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.98 (d, J= 8.4 Hz, 1H), 7.84 (m, 2H), 7.65 (dd, J= 2.4, 8.8 Hz, 1H), 7.52 (d, J= 2.8 Hz, 1H), 7.20 (d, J= 9.2 Hz, 1H), 7.08 (d, J= 8.4 Hz, 1H), 6.94 (q, J= 5 Hz, 1H), 6.74 (d, J= 2.8 Hz, 1H), 6.68 (dd, J= 2.8, 8.8 Hz, 1H), 4.68 (s, 3H), 4.00 (m, 2H), 3.10 (t, J= 8 Hz, 2H), 2.54 (d, J= 5 Hz), 2.01 (m, 5H). MS (ES): 617 (M^+).

__Example 110__



269

Step A:

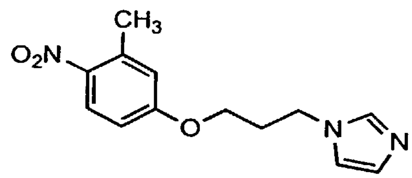


270

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed 2-methyl-3-nitrophenol (5.0 g, 0.033 mol), dibromopropane (26 mL, 52.7 g, 0.26 mol), potassium carbonate (6.8 g, 0.05 mol), and N, N-dimethylformamide (100 mL) and the mixture was allowed to stir at rt for 2.5 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, washed with water and brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting oil was distilled to afford **270**

(8.0 g, 89%) a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J= 9.2 Hz, 1H), 7.02 (d, J= 2.8 Hz, 1H), 6.96 (dd, J= 2.4, 8.8 Hz, 1H), 4.16 (t, J= 6 Hz, 2H), 3.63 (t, J= 6 Hz, 2H), 2.51 (s, 3H), 2.24 (m, 2H).

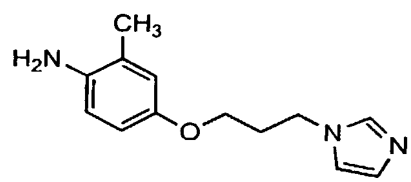
Step B:



271

Into a round-bottom flask equipped with a stir bar and nitrogen on demand were placed **270** (0.8 g, 2.9 mmol), imidazole (0.24 g, 3.49 mmol), potassium carbonate (0.8 g, 5.83 mmol), and N, N-dimethylformamide (20 mL) and the mixture was allowed to stir at 55 °C for 18 h. When judged to be complete, the reaction mixture was poured into a separatory funnel containing ethyl acetate and water. The organics were collected, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography eluding with 1:1 hexanes:ethyl acetate to afford **271** (0.3 g, 40%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J= 9 Hz, 1H), 7.65 (s, 1H), 7.22 (s, 1H), 7.04 (d, J= 2.4 Hz, 1H), 6.98 (dd, J= 2.7, 9 Hz, 1H), 6.92 (s, 1H), 4.16 (t, J= 7 Hz, 2H), 4.04 (t, J= 6 Hz, 2H), 2.57 (s, 3H), 2.22 (m, 2H).

Step C:



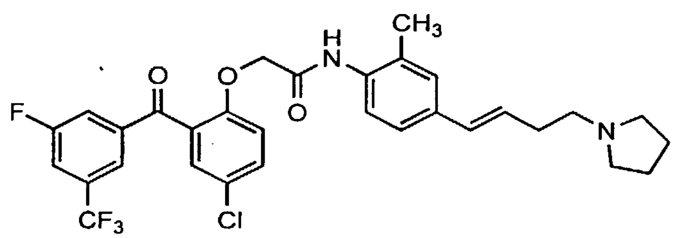
272

To a plastic-coated reaction vessel equipped with a stir bar, was added the nitro derivative **271** (0.3 g, 1.15 mmol), ethanol (20 mL), and palladium on charcoal (30 mg of 10% Pd/C, 10% w/w). The vessel was placed on a hydrogenation apparatus at 55 p.s.i. for 2 h. When judged to be complete, the reaction was filtered through a celite plug and the solvents were removed under reduced pressure to provide **272** (0.23 g, 88%) a purple oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (s, 1H), 7.14 (s, 1H), 6.85 (s, 1H), 6.54 (s, 1H), 6.48 (s, 2H), 4.44 (bs, 2H), 4.06 (t, J= 6.8 Hz, 2H), 3.70 (t, J= 6 Hz, 2H), 2.03 (m, 2H), 1.99 (s, 3H).

Step D:

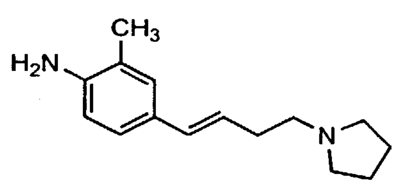
Acid **71** (120 mg, 0.32 mmol), oxalyl chloride (0.032 mL, 44 mg, 0.35 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **272** (67 mg, 0.29 mmol), $NaHCO_3$ (134 mg, 1.6 mmol), acetone (6 mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 5% MeOH:$CHCl_3$ as eluant to afford **269** (84 mg, 45%) as a pink solid. ^1H NMR (300 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.05 (d, J= 9 Hz, 1H), 7.90 (m, 2H), 7.71 (dd, J= 3, 9 Hz, 1H), 7.65 (s, 1H), 7.57 (d, J= 3Hz, 1H), 7.24 (m, 2H), 7.13 (d, J= 6Hz, 1H), 6.92 (s, 1H), 6.79 (d, J=3 Hz, 1H), 6.73 (dd, J= 3, 9 Hz, 1H), 4.74 (s, 2H), 4.14 (t, J= 6Hz, 2H), 3.88 (t, J= 6Hz, 2H), 2.16 (m, 2H), 2.03 (s, 3H). MS (ES): 589 (M^+), 590 $(M+H)^+$.

<u>**Example 111**</u>



272

Step A:



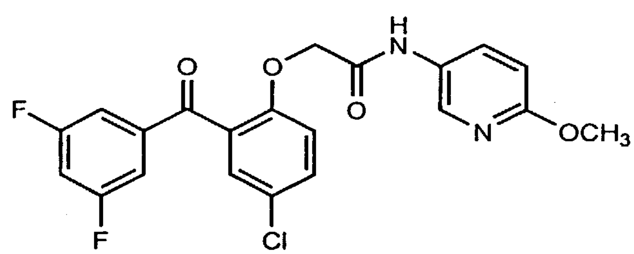
273

To a sealed-tube reaction vessel equipped with a stir bar and nitrogen on demand was added 4-bromo-2-methyl aniline (0.8 g, 4.3 mmol), palladium (II) acetate (97 mg, 0.43 mmol), tri-o-tolylphosphine (0.52 g, 1.72 mmol), N,N-dimethylformamide (15 mL), N-butylenepyrrolidine (2.7 g, 21.5 mmol), and triethylamine (4.2 mL, 3.0 g, 30.1 mmol). The tube was sealed and allowed to stir at 80 °C for 18 h. When judged to be complete, the reaction was filtered through a pad of celite and the filtrate was poured into ethyl acetate and water. The organics were collected and washed with water and brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The product was purified by flash chromatography using 93:7 $CHCl_3$: MeOH as eluant to provide **273**

(0.2 g, 20%) as a yellow oil. The product exists as a 2.7:1 mixture of E: Z isomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.87 (m, 2H), 6.51 (m, 1H), 6.18 (m, 1H), 5.87 (m, 1H), 4.81 (m, 2H), 2.44 (m, 8H), 2.31 (m, 2H), 2.00 (m, 2H), 1.85 (s, 3H). MS (ES): 231 $(M+H)^+$.

Step B:
Acid **71** (132 mg, 0.35 mmol), oxalyl chloride (0.034mL, 48 mg, 0.38 mmol), N,N-dimethylformamide (1 drop), and CH_2Cl_2 (10 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **273** (72 mg, 0.31 mmol), $NaHCO_3$ (152 mg, 1.7 mmol), acetone (6 mL), and water (0.5 mL) were used according to general procedure VI. The product was recrystallized from absolute ethanol to afford **272** (20 mg, 10%) as a white solid. The product exists as a 2.7:1 mixture of E:Z isomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (m, 1H), 7.98 (m, 1H), 7.85 (m, 2H), 7.65 (m, 1H), 7.51 (m, 1H), 7.20 (m, 4H), 6.32 (m, 1H), 6.21 (m, 1H), 4.72 (s, 2H), 2.46 (m, 8H), 2.31 (m, 2H), 2.04 (m, 2H), 1.65 (s, 3H). MS (ES): 590 $(M+H)^+$.

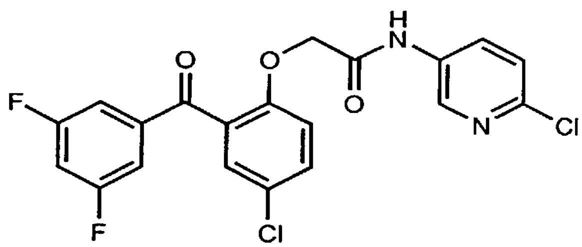
__Example 112__



274

The title compound was prepared according to General Procedure VI from acid **49** (0.51 mmol) and 5-amino-2-methoxypyridine (0.04 mL, 0.44 mmol). Purification by flash chromatography using 25% ethyl acetate/hexane as eluant, followed by trituration with ether gave **274** (0.146 g, 77%): mp 185-187 °C; MS (ES+) *m/z* 433 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1 H), 8.49 (d, 1 H), 8.09 (dd, 1 H), 7.56 (dd, 1 H), 7.41-7.38 (m, 3 H), 7.13-7.09 (m, 1 H), 7.05 (d, 1 H), 6.76 (d, 1 H), 4.72 (s, 2 H), 3.94 (s, 3 H).

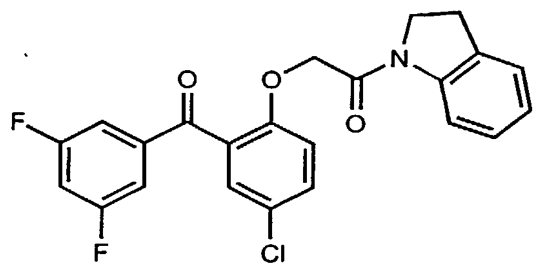
__Example 113__



275

The title compound was prepared according to General Procedure VI from acid **49** (0.51 mmol) and 5-amino-2-methoxypyridine (0.05 mL, 0.44 mmol). Purification by flash chromatography using 25% ethyl acetate/hexane as eluant followed by trituration with ether gave **275** (0.134 g, 70%): mp 198-200 °C; MS (ES+) *m/z* 437 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1 H), 8.80 (d, 1 H), 8.30 (dd, 1 H), 7.58 (dd, 1 H), 7.41 (dd, 1 H), 7.39-7.38 (m, 2 H), 7.32 (d, 1 H), 7.15-7.11 (m, 1 H), 7.07 (d, 1 H), 4.76 (s, 2 H).

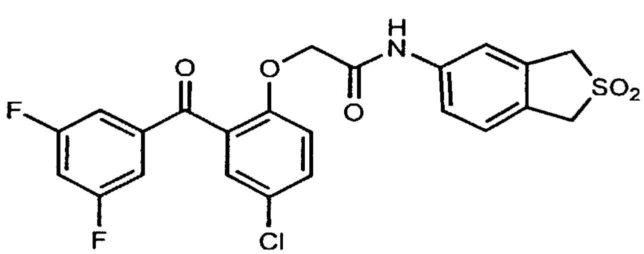
<u>**Example 114**</u>



276

The title compound was prepared according to General Procedure VI from acid **49** (0.51 mmol) and indoline (0.05 mL, 0.44 mmol). Purification by flash chromatography using 25% ethyl acetate/hexane as eluant followed by crystallization from methylene chloride/hexane gave **276** (0.069 g, 37%): mp 158-160 °C; MS (ES+) *m/z* 428 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 1 H), 7.44-7.39 (m, 4 H), 7.22-7.18 (m, 2 H), 7.07-6.97 (m, 3 H), 4.70 (s, 2 H), 3.98 (t, 2 H), 3.18 (t, 2 H) ppm.

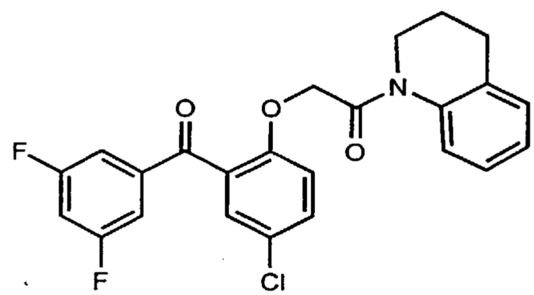
<u>**Example 115**</u>



277

The title compound was prepared according to General Procedure VI from acid **49** (0.51 mmol) and 5-amino-1,3-dihydro-benzo[c]thiophene-2,2-dioxide (0.081 g, 0.44 mmol). Purification by flash chromatography using 40-60% ethyl acetate/hexane as eluant followed by crystallization from ethyl acetate gave **277** (0.080 g, 37%): mp 197-199 °C; MS (ES-) *m/z* 490 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1 H), 7.92 (s, 1 H), 7.65 (dd, 1 H), 7.57 (dd, 1 H), 7.41-7.38 (m, 3 H), 7.30 (d, 1 H), 7.15-7.10 (m, 1 H), 7.05 (d, 1 H), 4.72 (s, 2 H), 4.39 (s, 2 H), 4.35 (s, 2 H).

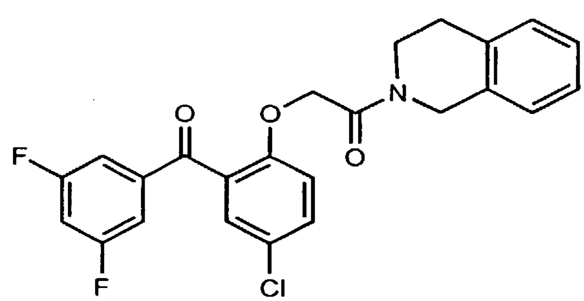
Example 116



278

The title compound was prepared according to General Procedure VI from acid **49** (0.49 mmol) and 1,2,3,4-tetrahydroquinoline (0.05 mL, 0.41 mmol). Isolation by flash chromatography using 15% ethyl acetate/hexane as eluant followed by trituration with hexanes gave **278** (0.081 g, 45%) in ca. 80% purity: MS (ES+) *m/z* 442 (M+H), 464 (M+Na); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, 1 H), 7.33-7.31 (m, 3 H), 7.11-7.09 (m, 3 H), 7.00-6.95 (m, 1 H), 6.88 (br s, 1 H), 4.73 (s, 2 H), 3.73 (br s, 2 H), 2.64 (br s, 2 H), 1.93-1.86 (m, 2 H).

Example 117

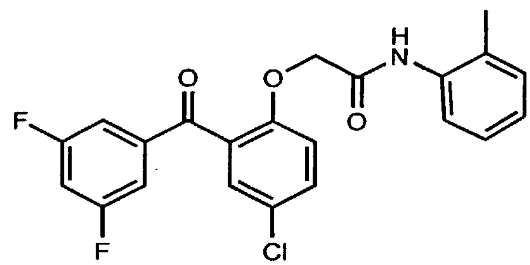


279

The title compound was prepared according to General Procedure VI from acid **49** (0.49 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.035 mL, 0.41 mmol). Isolation by flash

chromatography using 15% ethyl acetate/hexane as eluant followed by trituration with hexanes gave **279** (0.072 g, 40%) in ca. 80% purity: MS (ES+) *m/z* 442 (M+H), 464 (M+Na); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 1 H), 7.34-7.27 (m, 3 H), 7.19-7.15 (m, 2 H), 7.13-7.08 (m, 2 H), 7.02-6.93 (m, 2 H), 4.70 (s, 2 H), 4.65 (s, 1 H), 4.46 (s, 1 H), 3.73 (t, 1 H), 3.57 (t, 1 H), 2.81-2.75 (m, 2 H).

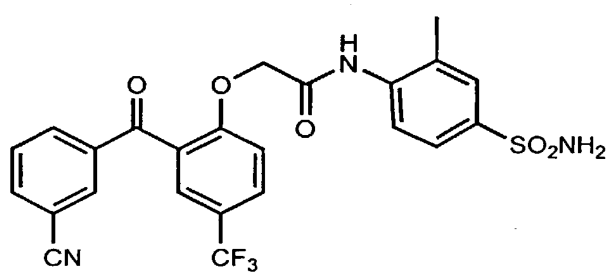
Example 118



280

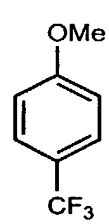
The title compound was prepared according to General Procedure VI from acid **49** (0.50 mmol) and *o*-toluidine (0.05 mL, 0.43 mmol). Isolation by flash chromatography using 10% ethyl acetate/hexane as eluant gave **280** (0.121 g, 58%): MS (ES+) *m/z* 416 (M+H), 438 (M+Na); MS (ES-) *m/z* 414 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1 H), 7.71 (d, 1 H), 7.53 (dd, 1 H), 7.36 (d, 1 H), 7.34-7.31 (m, 2 H), 7.22-7.17 (m, 2 H), 7.09 (app t, 1 H), 7.05 –7.01 (m, 2 H), 4.77 (s, 2 H), 2.18 (s, 3 H) ppm.

Example 119



281

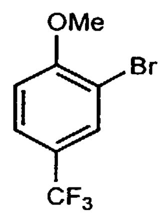
Step A:



282

A mixture of trifluoro-*p*-cresol (18.9 g, 117 mmol), potassium carbonate (16.4 g, 119 mmol) and iodomethane (9.8 mL, 158 mmol) in 200 mL acetone was warmed to reflux for 8.5 h, then stirred at room temperature an additional 16 h. The reaction mixture was then concentrated *in vacuo*, and the residue was partitioned between 150 mL water and 150 mL ethyl acetate. The aqueous layer was extracted with another 150 mL of ethyl acetate, and the combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **282** (18.97 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 2H), 6.96 (d, 2 H), 3.85 (s, 3 H).

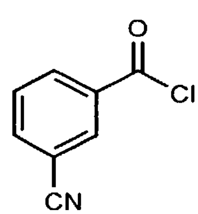
Step B:



283

Bromine (4.1 mL, 79 mmol) was added dropwise to a solution of **282** (13.2 g, 75.2 mmol) and sodium acetate (6.48 g, 79 mmol) in 150 mL of glacial acetic acid over 35 min. The reaction mixture was stirred an additional 23 h at room temperature, then 10% $NaHSO_3$ (aq) was added until the orange reaction mixture became colorless. The mixture was then extracted with two 150-mL portions of CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 26.48 g of crude material. Purification by flash chromatography using 2% ethyl acetate/hexane as eluant gave **283** (2.232 g, 12%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 1 H), 7.53 (dd, 1 H), 6.94 (d, 1 H), 3.93 (s, 3 H) ppm.

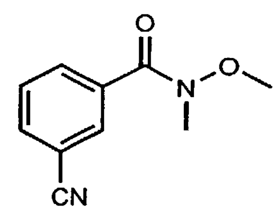
Step C:



284

Oxalyl chloride (48 mL, 96.5 mmol) was added dropwise over 1 h to a solution of 3-cyanobenzoic acid (5.767 g, 38.6 mmol) in 200 mL of CH_2Cl_2 and 0.10 mL of DMF, and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo* to give **284** (8.516 g), which was used immediately without further purification or characterization.

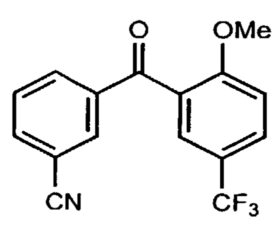
Step D:



285

A solution of N,O-dimethylhydroxylamine (4.90 g, 50.2 mmol) in 20 mL of triethylamine and 100 mL of chloroform was cooled to 0 °C, and **284** (8.52 g, 38.6 mmol) was added dropwise over 10 min. The resulting mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature over 1.25 h. The reaction mixture was diluted with 150 mL ethyl acetate and washed with two 100-mL portions of water and a small portion of brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 285 (6.381 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1 H), 7.95 (d, 1 H), 7.75 (d, 1 H), 7.55 (dd, 1 H), 3.54 (s, 3 H), 3.39 (s, 3 H).

Step E:

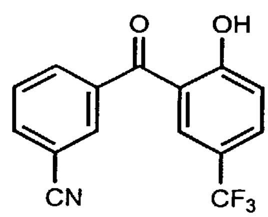


286

n-Butyl lithium (7.7 mL of 1.6 M solution in hexanes) was added dropwise to a solution of **283** (2.735 g, 10.7 mmol) in 40 mL of ether at −78 °C over 15 min. The reaction mixture was stirred at −78 °C for an additional 15 min, then a solution of **285** (2.24 g, 11.8 mmol) in 15 mL of ether was added dropwise over 20 min. The resulting mixture was stirred for

1 h at –78 °C, then allowed to warm to room temperature and continue stirring for 4.67 h. The reaction mixture was quenched with the slow addition of 20 mL of water, stirred open to air for 45 minutes, and partitioned between 100 mL of ether and 100 mL of water. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 4.036 g of an orange liquid. Purification by flash chromatography using 5-10% ethyl acetate/hexane as eluant gave **286** (1.850 g, 57%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.99 (m, 2 H), 7.83 (d, 1 H), 7.78 (d, 1 H), 7.67 (s, 1 H), 7.59 (dd, 1 H), 7.08 (d, 1 H), 3.76 (s, 3 H).

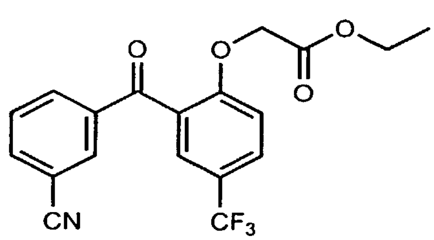
Step F:



287

The title compound (1.781 g, 100%) was prepared according to General Procedure IX from the anisole derivative **286** (1.805 g, 5.91 mmol). This intermediate was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1 H), 7.97 (s, 1 H), 7.92 (d, 1 H), 7.87 (d, 1 H), 7.77 (dd, 1 H), 7.73 (s, 1 H), 7.69 (t, 1 H), 7.21 (d, 1 H).

Step G:

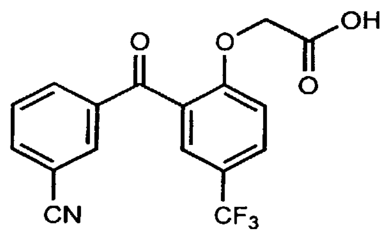


288

The title compound (2.196 g, 100%) was prepared according to General Procedure II from the phenol derivative **287** (1.78 g, 5.91 mmol). This intermediate was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1 H), 8.09 (d, 1 H), 7.82 (d, 1 H), 7.74

(d, 1 H), 7.73 (s, 1 H), 7.58 (t, 1 H), 6.90 (d, 1 H), 4.58 (s, 2 H), 4.20 (q, 2 H), 1.24 (t, 3 H).

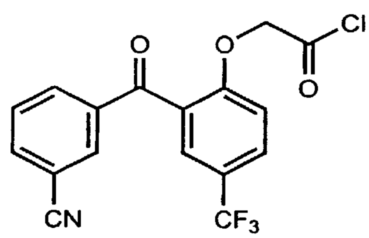
Step H:



289

The title compound (1.758 g, 85%) was prepared according to General Procedure III from the ester derivative **288** (2.2 g, 5.91 mmol). This intermediate was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 8.11 (d, 1 H), 7.90 (d, 1 H), 7.78 (dd, 1 H), 7.69 (d, 1 H), 7.64 (t, 1 H), 7.12 (d, 1 H), 4.86 (s, 2 H).

Step I:



290

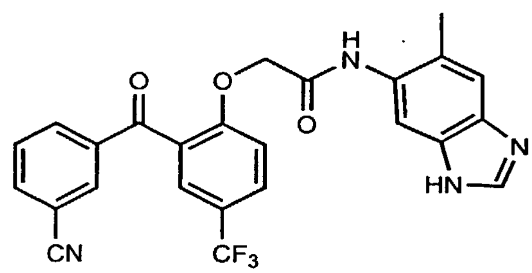
The title compound (0.432 g) was prepared according to General Procedure V from the acid derivative **289** (0.345 g, 0.99 mmol). This intermediate was used immediately without further purification or characterization.

Step J:

Compound **281** was prepared according to the General Procedure VI from the acid chloride **290** (0.49 mmol) and the aniline derivative **466** (0.076 g, 0.41 mmol). Purification by flash chromatography using 1% methanol/methylene chloride as eluant gave **281** (0.113 g, 53%): MS (ES+) *m/z* 516 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1 H), 8.20 (s, 1 H), 8.10-8.06 (m, 2 H), 7.94 (dd, 1 H), 7.80 (d, 1 H), 7.70 (app t, 1

H), 7.65-7.62 (m, 2 H), 7.57 (dd, 1 H), 7.36 (d, 1 H), 7.24 (s, 2 H), 4.90 (s, 2 H), 2.17 (s, 3 H).

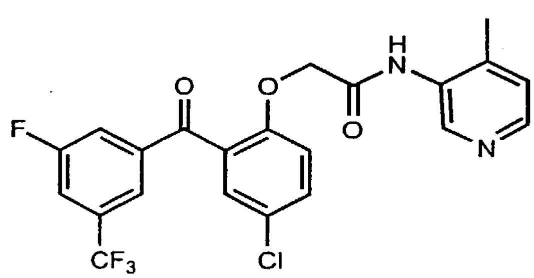
Example 120



291

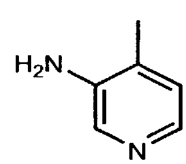
Compound **291** was prepared according to General Procedure VI from the acid chloride **290** (0.49 mmol) and the aniline derivative **210** (0.060 g, 0.41 mmol). Purification by flash chromatography using 1-3% methanol/methylene chloride, followed by crystallization from methylene chloride/hexane gave **291** (0.046 g, 20%): MS (ES+) *m/z* 479 (M+H); MS (ES-) *m/z* 477 (M-H); ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 –8.16 (m, 2 H), 8.07 (d, 1 H), 7.94-7.89 (m, 2 H), 7.79 (d, 1 H), 7.65 (app t, 1 H), 7.62 (s, 1 H), 7.44-7.41 (m, 2 H), 4.85 (s, 2 H), 2.20 (s, 3 H).

Example 121



292

Step A:



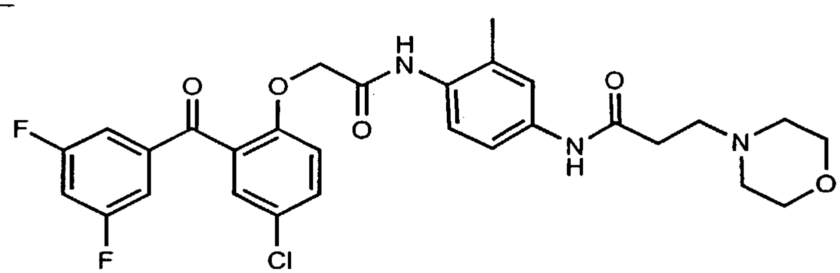
293

A mixture of 4-methyl-3-nitropyridine (1.102 g, 7.24 mmol) and 10% palladium on carbon (0.096 g) in 20 mL of methanol was stirred at room temperature under an atmosphere of 49 psi hydrogen gas for 2 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **293** (0.849 g, quant.): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.92 (d, 1 H), 6.93 (d, 1 H), 3.59 (br s, 2 H), 2.14 (s, 3 H).

Step B:

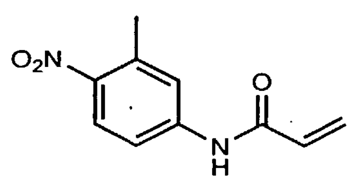
Compound **292** was prepared according to the General Procedure IV from the acid 71 (0.188 g, 0.5 mmol) and the aminopyridyl derivative **293** (0.065 g, 0.6 mmol). Purification by flash chromatography using 0.5-2% methanol/methylene chloride as eluant gave **292** (0.071 g, 30%) as a white solid: MS (ES+) *m/z* 467 (M+H); MS (ES-) *m/z* 465 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1 H), 8.65 (s, 1 H), 8.35 (d, 1 H), 7.88 (s, 1 H), 7.70 (d, 1 H), 7.62-7.58 (m, 2 H), 7.40 (d, 1 H), 7.16 (d, 1 H), 7.10 (d, 1 H), 4.76 (s, 2 H), 2.26 (s, 3 H) ppm.

Example 122



294

Step A:

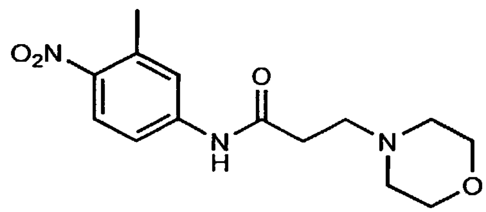


295

A mixture of 3-methyl-4-nitroaniline (1.052 g, 6.91 mmol) and triethylamine (1.16 mL, 8.29 mmol) in 20 mL of methylene chloride was cooled to 0 °C and acryloyl chloride (0.62 mL, 7.61 mmol) was added dropwise over 5 min. The resulting mixture was stirred

an additional 1.5 h at 0 °C, then diluted with 35 mL of methylene chloride, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give **295** (1.941 g) which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (br s, 1 H), 8.01 (d, 1 H), 7.75 (d, 1 H), 7.65 (dd, 1 H), 6.49-6.40 (m, 2 H), 5.78 (dd, 1 H), 2.60 (s, 3 H).

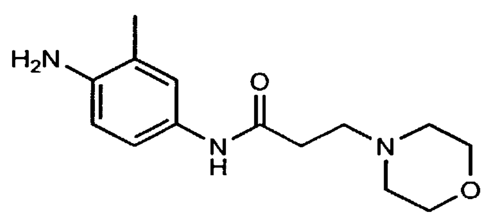
Step B:



296

A mixture of compound **295** (6.91 mmol) and morpholine (0.63 mL, 7.26 mmol) in 25 mL of ethanol was warmed to reflux for 2.3 h. The reaction mixture was then concentrated *in vacuo*, suspended in ethyl acetate, and filtered. The filtrate was concentrated *in vacuo*, dissolved in ethyl acetate, and allowed to crystallize. The crystalline impurity was removed by filtration, and the filtrate was concentrated *in vacuo* to give **296** (1.767 g, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (br s, 1 H), 8.03 (d, 1 H), 7.54 (d, 1 H), 7.43 (dd, 1 H), 3.84-3.82 (m, 4 H), 2.76-2.73 (m, 2 H), 2.64 (br s, 4 H), 2.62 (s, 3 H), 2.58-2.55 (m, 2 H) ppm.

Step C:



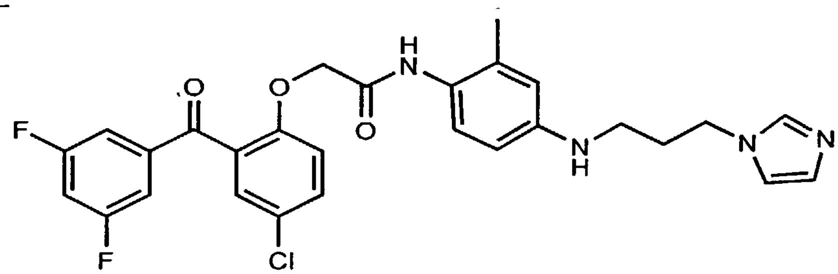
297

A mixture of compound **296** (0.202 g, 0.69 mmol) and 10% palladium on carbon (0.018 g) in 10 mL of methanol was stirred at room temperature under an atmosphere of 53 psi hydrogen gas for 2.17 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **297** (0.192 g, quant.): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (br s, 1 H), 7.38 (s, 1 H), 7.27 (dd, 1 H), 6.76 (s, 1 H), 3.97-3.92 (m, 4 H), 2.91-2.83 (m, 2 H), 2.77-2.72 (m, 4 H), 2.66-2.62 (m, 2 H), 2.25 (s, 3 H).

Step D:

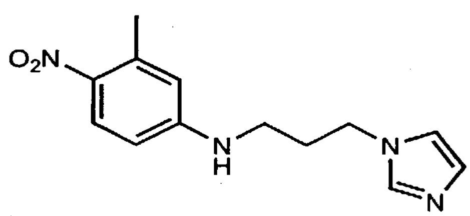
Compound **294** was prepared according to the General Procedure VI from the acid chloride **49** (0.5 mmol) and the aniline derivative **297** (0.180 g, 0.68 mmol). Purification by flash chromatography using 1-2% methanol/methylene chloride as eluant gave **294** (0.203 g, 71%): MS (ES-) *m/z* 570 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1 H), 8.27 (s, 1 H), 7.57 (d, 1 H), 7.52-7.48 (m, 2 H), 7.35 (d, 1 H), 7.31-7.30 (m, 2 H), 7.22-7.20, (d, 1 H), 7.04-7.00 (m, 2 H), 4.64 (s, 2 H), 3.77 (br s, 4 H), 2.71-2.68 (m, 2 H), 2.57 (br s, 4 H), 2.50-2.47 (m, 2 H), 2.14 (s, 3 H).

__Example 123__



298

Step A:

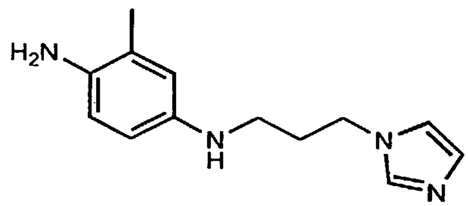


299

A mixture of 5-fluoro-2-nitrotoluene (0.24 mL, 2.0 mmol), 1-(3-aminopropyl)-imidazole (0.41 mL, 3.4 mmol), and sodium bicarbonate (0.302 g, 3.6 mmol) in 5 mL of pyridine and 0.5 mL of water was heated to reflux for 3 h. The reaction mixture was then partitioned between 50 mL of water and 50 mL of ethyl acetate. The organic layer was concentrated to give a yellow solid, which was purified by crystallization from ethyl acetate/hexane to provide **299** (0.255 g, 49%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 1

H), 7.60 (s, 1 H), 7.16 (s, 1 H), 7.08 (t, 1 H), 6.87 (s, 1 H), 6.47 (dd, 1 H), 6.40 (d, 1 H), 4.04-3.98 (m, 2 H), 3.06-3.01 (m, 2 H), 2.47 (s, 3 H), 1.98-1.91 (m, 2 H).

Step B:



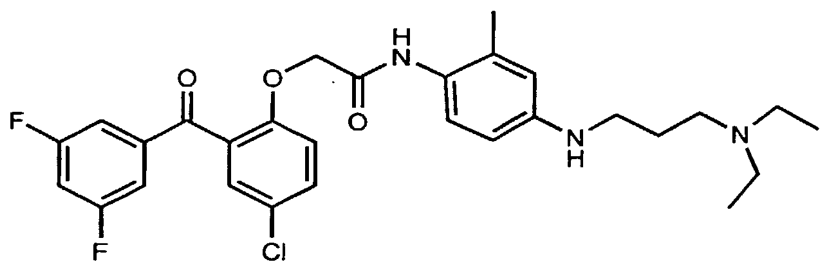
300

A mixture of compound **299** (0.233 g, 0.90 mmol) and 10% palladium on carbon (0.020 g) in 20 mL of methanol was stirred at room temperature under an atmosphere of 53 psi hydrogen gas for 1 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **300** (0.166 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1 H), 7.07 (s, 1 H), 6.92 (s, 1 H), 6.58 (d, 1 H), 6.40 (d, 1 H), 6.36 (dd, 1 H), 4.08 (t, 2 H), 3.49-3.48 (m, 1 H), 3.26 (br s, 2 H), 3.08-3.05 (m, 2 H), 2.13 (s, 3 H), 2.08-2.02 (m, 2 H).

Step C:

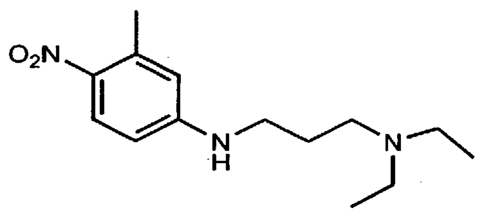
Compound **298** was prepared according to the General Procedure IV from the acid **49** (0.196 g, 0.6 mmol) and the aniline derivative **300** (0.155 g, 0.67 mmol). Purification by flash chromatography using 2% methanol/methylene chloride as eluant gave **298** (0.219 g, 68%): MS (ES+) *m/z* 539 (M+H); MS (ES-) *m/z* 537 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.55 (dd, 1 H), 7.49 (s, 1 H), 7.39 (d, 1 H), 7.35-7.31 (m, 2 H), 7.30 (d, 1 H), 7.08 (s, 1 H), 7.06-7.01 (m, 2 H), 6.93 (s, 1 H), 6.43-6.40 (m, 2 H), 4.67 (s, 2 H), 4.09-4.06 (m, 2 H), 3.54 (br s, 1 H), 3.11 (t, 2 H), 2.11-2.06 (m, 5 H).

Example 124



301

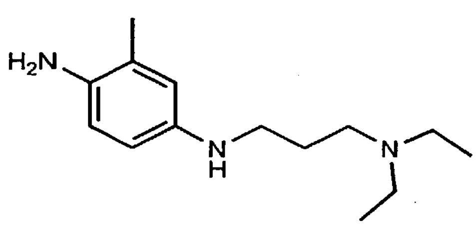
Step A:



302

A mixture of 5-fluoro-2-nitrotoluene (0.37 mL, 3.0 mmol), N,N-diethyl-1,3-propanediamine (0.80 mL, 5.1 mmol), and sodium bicarbonate (0.454 g, 5.4 mmol) in 7.5 mL of pyridine and 0.75 mL of water was heated to reflux for 3 h. The reaction mixture was stirred at room temperature an additional 3 h, then partitioned between 50 mL of water and 50 mL of ethyl acetate. The aqueous layer was extracted with an additional 20 mL of ethyl acetate, and the combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.833 g of crude material. Purification by flash chromatography using 1-5% methanol/methylene chloride as eluant gave **302** (0.742 g, 93%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 1 H), 6.66 (br s, 1 H), 6.34 (dd, 1 H), 6.27 (d, 1 H), 3.29-3.25 (m, 2 H), 2.61 (s, 3 H), 2.60-2.51 (m, 6 H), 1.81-1.75 (m, 2 H), 1.06 (t, 6 H).

Step B:



303

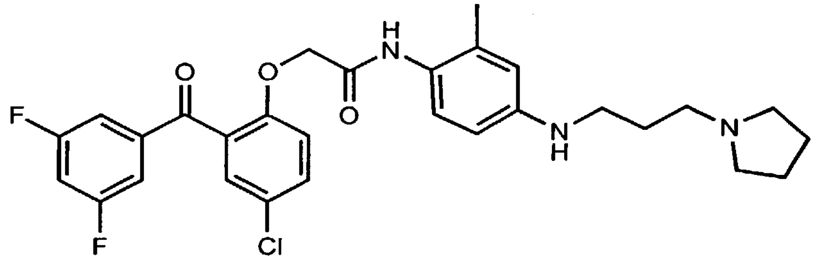
A mixture of compound **302** (0.730 g, 2.75 mmol) and 10% palladium on carbon (0.070 g) in 20 mL of methanol was stirred at room temperature under an atmosphere of 55 psi

hydrogen gas for 1.17 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **303** (0.581 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, 1 H), 6.42-6.37 (m, 2 H), 3.11-3.08 (m, 2 H), 2.54-2.49 (m, 6 H), 2.14 (s, 3 H), 1.78-1.71 (m, 2 H), 1.03 (t, 6 H).

Step C:

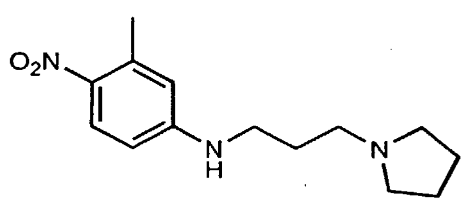
Compound **301** was prepared according to the General Procedure IV from the acid **49** (0.196 g, 0.6 mmol) and the aniline derivative **303** (0.158 g, 0.67 mmol). Purification by flash chromatography using 3% methanol/0.1% triethylamine/methylene chloride as eluant, followed by crystallization from ethyl acetate/hexane gave **301** (0.113 g, 35%): MS (ES+) *m/z* 544 (M+H); MS (ES-) *m/z* 542 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br s, 1 H), 7.54 (dd, 1 H), 7.39 (d, 1 H), 7.34-7.31 (m, 2 H), 7.25 (d, 1 H), 7.05-6.99 (m, 2 H), 6.43-6.41 (m, 2 H), 4.65 (s, 2 H), 3.15 (t, 2 H), 2.57-2.52 (m, 6 H), 2.07 (s, 3 H), 1.80-1.73 (m, 2 H), 1.05 (t, 6 H).

Example 125



304

Step A:

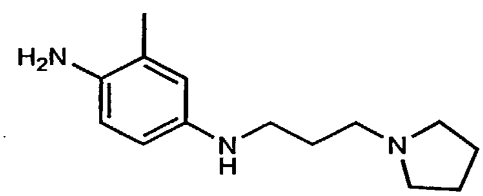


305

A mixture of 5-fluoro-2-nitrotoluene (0.37 mL, 3.0 mmol), 1-(3-aminopropyl)pyrrolidine (0.64 mL, 5.1 mmol), and sodium bicarbonate (0.454 g, 5.4 mmol) in 7.5 mL of pyridine and 0.75 mL of water was heated to reflux for 3 h. The reaction mixture was stirred at

room temperature an additional 3 h, then partitioned between 50 mL of water and 50 mL of ethyl acetate. The aqueous layer was extracted with an additional 20 mL of ethyl acetate, and the combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.758 g of crude material. Purification by flash chromatography using 0.5-10% methanol/methylene chloride as eluant gave **305** (0.595 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 1 H), 6.35 (dd, 1 H), 6.29 (d, 1 H), 6.09 (br s, 1 H), 3.30-3.26 (m, 2 H), 2.65-2.62 (m, 2 H), 2.61 (s, 3 H), 2.58-2.52 (m, 4 H), 1.86-1.78 (m, 6 H).

Step B:



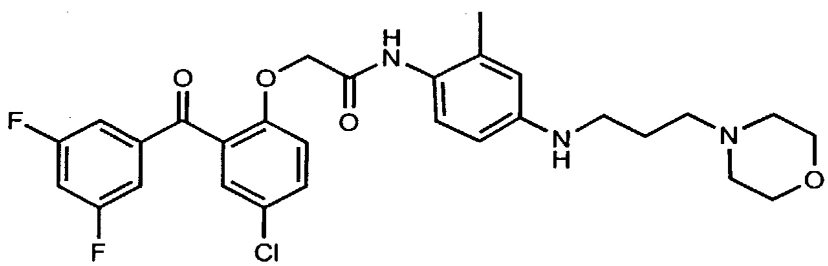
306

A mixture of compound **305** (0.590 g, 2.24 mmol) and 10% palladium on carbon (0.060 g) in 20 mL of methanol was stirred at room temperature under an atmosphere of 60 psi hydrogen gas for 1.33 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give **306** (0.520 g, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, 1 H), 6.42 (d, 1 H), 6.39 (dd, 1 H), 3.23 (br s, 2 H), 3.12 (t, 2 H), 2.56 (t, 2 H), 2.53-2.48 (m, 4 H), 2.13 (s, 3 H), 1.84-1.75 (m, 6 H) ppm.

Step C:

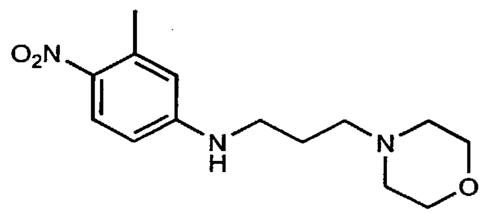
Compound **304** was prepared according to the General Procedure IV from the acid **49** (0.196 g, 0.6 mmol) and the aniline derivative **306** (0.156 g, 0.67 mmol). Purification by flash chromatography using 3% methanol/0.1% triethylamine/methylene chloride as eluant, followed by crystallization from ethyl acetate/hexane gave **304** (0.064 g, 20%): MS (ES+) *m/z* 542 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.54 (dd, 1 H), 7.39 (d, 1 H), 7.36-7.31 (m, 2 H), 7.26 (s, 1 H), 7.05-7.00 (m, 2 H), 6.44-6.42 (m, 2 H), 4.65 (s, 2 H), 3.18 (t, 2 H), 2.65-2.59 (m, 6 H), 2.07 (s, 3 H), 1.87-1.79 (m, 6 H).

Example 126



307

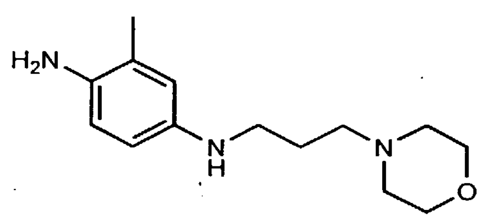
Step A:



308

A mixture of 5-fluoro-2-nitrotoluene (0.24 mL, 2.0 mmol), 4-(3-aminopropyl)morpholine (0.50 mL, 3.4 mmol), and sodium bicarbonate (0.302 g, 3.6 mmol) in 5 mL of pyridine and 0.5 mL of water was heated to reflux for 1 h. The reaction mixture was then partitioned between 50 mL of water and 50 mL of ethyl acetate, and the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.493 g of crude material. Purification by flash chromatography using 1% methanol/methylene chloride as eluant gave **308** (0.279 g, 50%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 1 H), 6.38 (dd, 1 H), 6.31 (s, 1 H), 5.92 (br s, 1 H), 3.77-3.75 (m, 4 H), 3.31-3.27 (m, 2 H), 2.6 (s, 3 H), 2.54-2.50 (m, 6 H), 1.85-1.79 (m, 2 H).

Step B:



309

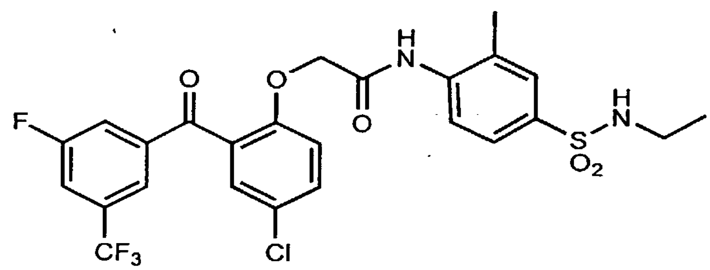
A mixture of compound **308** (0.266 g, 0.95 mmol) and 10% palladium on carbon (0.020 g) in 5 mL of methanol was stirred at room temperature under an atmosphere of 60 psi hydrogen gas for 2 h. The reaction mixture was then filtered through Celite and

concentrated *in vacuo* to give **309** (0.229 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, 1 H), 6.43 (d, 1 H), 6.39 (dd, 1 H), 3.74-3.72 (m, 4 H), 3.14-3.11 (m, 2 H), 2.48-2.45 (m, 6 H), 2.14 (s, 3 H), 1.81-1.75 (m, 2 H).

Step C:

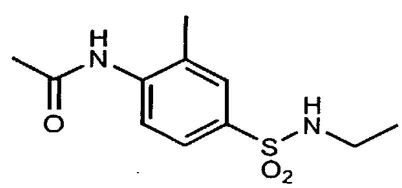
Compound **307** was prepared according to the General Procedure IV from the acid **49** (0.092 g, 0.28 mmol) and the aniline derivative **309** (0.070 g, 0.28 mmol). Purification by flash chromatography using 3% methanol/0.1% triethylamine/methylene chloride as eluant gave **307** (0.101 g, 65%): MS (ES+) *m/z* 558 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.54 (dd, 1 H), 7.40-6.72 (m, 6 H), 6.62 (d, 1 H), 6.45-6.42 (m, 2 H), 4.66 (s, 2 H), 3.75-3.61 (m, 4 H), 3.17 (t, 2 H), 2.49-2.25 (m, 6 H), 2.08 (s, 3 H), 1.82-1.51 (m, 2 H).

Example 127



310

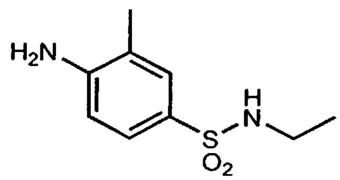
Step A:



311

A mixture of sulfonyl chloride **464** (1.10 g, 4.4 mmol), ethylamine (3.3 mL of 2.0 M THF solution, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at room temperature for 11 d. The reaction mixture was then diluted with 50 mL of water and filtered to give 0.605 g of crude material. Crystallization from methanol gave **311** (0.425 g, 38%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1 H), 7.73 (d, 1 H), 7.58 (d, 1 H), 7.53 (dd, 1 H), 7.39 (t, 1 H), 2.75-2.68 (m, 2 H), 2.26 (s, 3 H), 2.07 (s, 3 H), 0.93 (t, 3 H).

Step B:



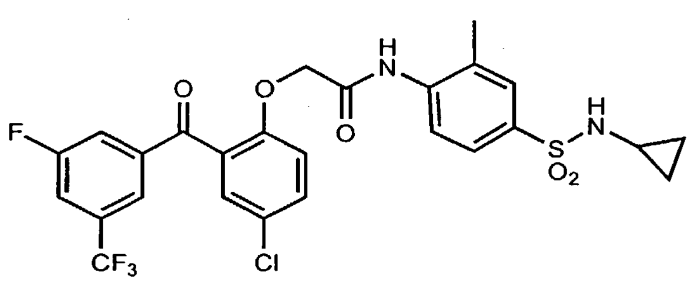
312

A mixture of compound **311** (0.308 g, 1.2 mmol), 1.5 M HCl (2.5 mL), and ethanol (12 mL) was heated to 80 °C for 18 h, then stirred at room temperature an additional 1 h. The reaction mixture was poured into 50 mL saturated $NaHCO_3$ (aq) and extracted with two 30-mL portions of methylene chloride. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **312** (0.337 g), which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2 H), 6.68 (d, 1 H), 4.29 (t, 1 H), 4.07 (br s, 2 H), 3.00-2.93 (m, 2 H), 2.18 (s, 3 H), 1.10 (t, 3 H).

Step C:

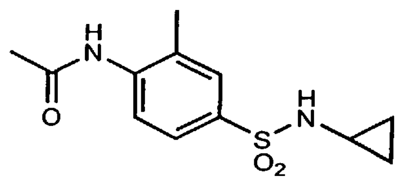
Compound **310** was prepared according to the General Procedure IV from the acid **71** (0.188 g, 0.5 mmol) and the aniline derivative **312** (0.169 g, 0.6 mmol). Purification by flash chromatography using 15-25% ethyl acetate/hexane as eluant gave **310** (0.016 g, 6%): MS (ES+) *m/z* 573 (M+H); MS (ES-) *m/z* 571 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1 H), 8.08 (d, 1 H), 7.88 (s, 1 H), 7.69 (m, 3 H), 7.59 (dd, 2 H), 7.38 (d, 1 H), 7.09 (d, 1 H), 4.74 (s, 2 H), 3.03-2.95 (m, 2 H), 2.31 (s, 3 H), 1.11 (t, 3 H).

<u>**Example 128**</u>



313

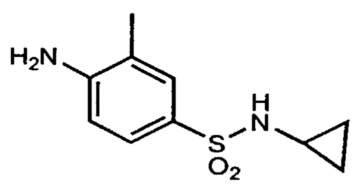
Step A:



314

A mixture of sulfonyl chloride **464** (1.10 g, 4.4 mmol), cyclopropylamine (0.46 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at room temperature for 6 d. The reaction mixture was then filtered to give 0.800 g of crude material. Crystallization from methanol gave **314** (0.329 g, 28%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1 H), 7.78 (s, 1 H), 7.77-7.60 (m, 2 H), 7.56 (dd, 1 H), 2.27 (s, 3 H), 2.08 (s, 3 H), 2.06-2.03 (m, 1 H), 0.45-0.42 (m, 2 H), 0.36-0.34 (m, 2 H).

Step B:



315

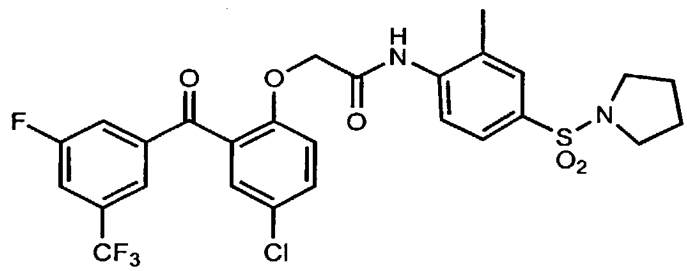
A mixture of compound **314** (0.324 g, 1.2 mmol), 1.5 M HCl (2.5 mL), and ethanol (12 mL) was heated to 80 °C for 18 h, then stirred at room temperature an additional 1 h. The reaction mixture was poured into 25 mL saturated $NaHCO_3$ (aq) and extracted with two 25-mL portions of methylene chloride. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **315** (0.256 g, 94%), which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2 H), 6.69 (d, 1 H), 4.81 (br s, 2 H), 2.22-2.19 (m, 4 H), 0.59-0.55 (m, 4 H).

Step C:

Compound **313** was prepared according to the General Procedure IV from the acid **71** (0.188 g, 0.5 mmol) and the aniline derivative **315** (0.124 g, 0.55 mmol). Purification by flash chromatography using 15-25% ethyl acetate/hexane as eluant gave **313** (0.026 g, 9%): MS (ES+) *m/z* 585 (M+H); MS (ES-) *m/z* 583 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1 H), 8.12 (d, 1 H), 7.88 (s, 1 H), 7.75-7.71 (m, 3 H), 7.59 (dd, 2 H), 7.47-7.43 (m,

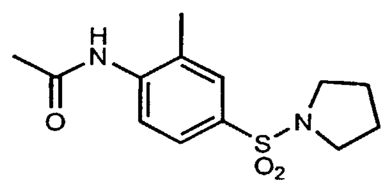
1 H), 7.38 (d, 1 H), 7.08 (d, 1 H), 4.75 (s, 2 H), 2.32 (s, 3 H), 2.25-2.19 (m, 1 H), 0.63-0.57 (m, 4 H).

Example 129



316

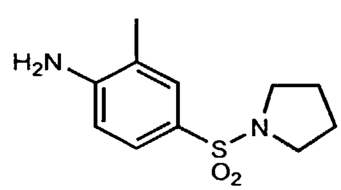
Step A:



317

A mixture of sulfonyl chloride **464** (1.10 g, 4.4 mmol), pyrrolidine (0.55 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at room temperature for 6 d. The reaction mixture was then filtered, and the filter cake was washed with methylene chloride and methanol and dried with a vacuum pump to give **317** (0.696 g, 56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1 H), 7.82 (d, 1 H), 7.60 (d, 1 H), 7.55 (dd, 1 H), 3.10-3.07 (m, 4 H), 2.28 (s, 3 H), 2.09 (s, 3 H), 1.64-1.58 (m, 4 H).

Step B:



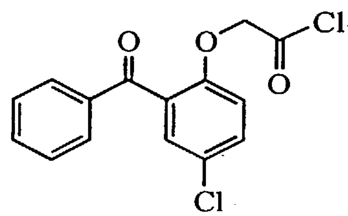
318

A mixture of compound **317** (0.690 g, 2.44 mmol), 1.5 M HCl (5.0 mL), and ethanol (25 mL) was heated to 80 °C for 18 h, then stirred at room temperature an additional 7 h. The reaction mixture was filtered to give **318** (0.369 g, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.29-7.26 (m, 2 H), 6.64 (d, 1 H), 5.73 (br s, 2 H), 3.01-2.98 (m, 4 h), 2.05 (s, 3 H), 1.60-1.56 (m, 4 H).

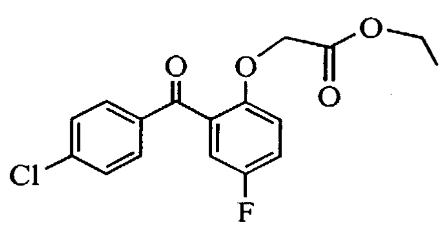
Step C:

Compound **316** was prepared according to the General Procedure IV from the acid **71** (0.188 g, 0.5 mmol) and the aniline derivative **318** (0.132 g, 0.55 mmol). Purification by flash chromatography using 15-25% ethyl acetate/hexane as eluant gave **316** (0.013 g, 4%): MS (ES+) *m/z* 599 (M+H); MS (ES-) *m/z* 597 (M-H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1 H), 7.97-7.01 (m, 9 H), 4.78 (s, 2 H), 3.08-3.04 (m, 4 H), 2.15 (s, 3 H), 1.59-1.56 (m, 4 H).



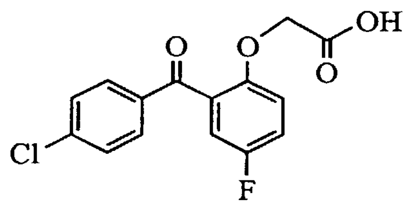
320

Carboxylic acid **105** (5 g, 17 mmol), methylene chloride (90 mL), and thionyl chloride (13.2 mL, 18 mmol) were used as described in general procedure XV to afford **320** as an orange oil (5.31 g). The crude product was used without further purification.



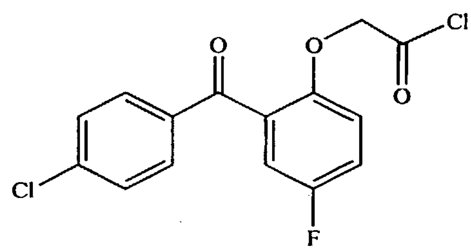
321

4'-Chloro-5-fluoro-2-hydroxybenzophenone (Lancaster, 5 g, 20 mmol), potassium carbonate (13.8 g, 100 mmol), ethyl bromoacetate (2.5 mL, 23 mmol), and acetone (200 mL) were used as in general procedure II to afford **321** as an orange/off-white solid (6.72 g, crude material). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.2 (t, 3H), 4.1 (m, 2H), 4.75 (s, 2H), 7.15 (dd, 1H), 7.3 (dd, 1H), 7.35-7.4 (m, 1H), 7.6 (d, 2H), 7.8 (d, 2H).



322

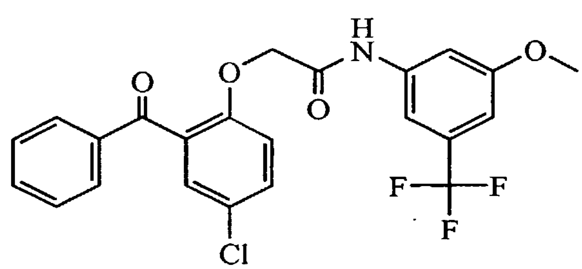
Ester **321** (6.72 g, 20 mmol), ethanol (80 mL), water (20 mL), and lithium hydroxide monohydrate (1 g, 24 mmol) were used as in general procedure III to afford carboxylic acid **322** as off-white solid (6.56 g, crude material). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 7.1 (d, 1H), 7.3 (d, 1H), 7.4 (m, 1H), 7.6 (d, 2H), 7.8 (d, 2H), 13 (bs, 1H); MS (ES$^-$) *m/z* 307 (M-H)$^-$.



323

Into a round-bottom flask were placed acid **322** (3 g, 10 mmol) and thionyl chloride (51 mL of a 2N solution in methylene chloride, 102 mmol). After refluxing for 1 1/2 h, the mixture was concentrated in vacuo to give **323** as a dark purple oil, which was used without characterization or purification.

Example 130

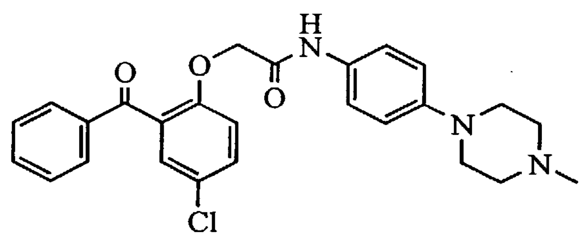


324

3-Methoxy-5-(trifluoromethyl)aniline (Aldrich, 0.309 g, 1.62 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (7

mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 9:1 and 4:1 hexanes:ethyl acetate to afford **324** as an off-white solid (0.17 g, 23%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.8 (s, 3H), 4.7 (s, 2H), 7 (s, 1H), 7.2 (d, 1H), 7.4 (s, 1H), 7.5 (m, 4H), 7.6 (m, 2H), 7.8 (d, 2H), 10 (s, 1H); MS (ES$^-$) *m/z* 462 (M-H)$^-$.

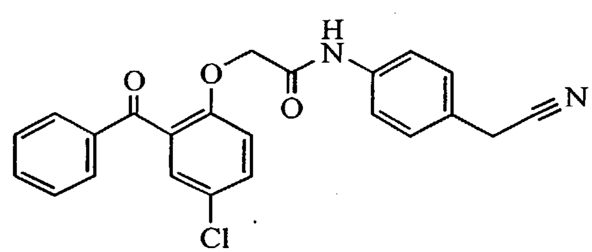
Example 131



325

4-(N-Methylpiperazinyl)aniline (Biomet Research Ltd., 0.237 g, 1.24 mmol), NEt_3 (0.26 mL, 1.87 mmol), acetonitrile (5 mL), and acid chloride **320** (0.38 g, 1.24 mmol) in acetonitrile (2 mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 49:1 and 24:1 methylene chloride:methanol to afford **325** as a yellow solid (0.16 g, 27%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.2 (s, 3H), 2.4 (t, 4H), 3.1 (t, 4H), 4.7 (s, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.3 (d, 2H), 7.5 (s, 1H), 7.55 (t, 2H), 7.6-7.7 (m, 2H), 7.8 (d, 2H) 9.5 (s, 1H); MS (ES$^-$) *m/z* 462 (M-H)$^-$.

Example 132

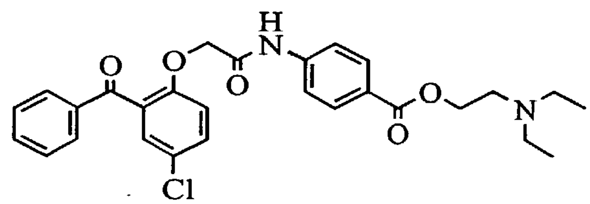


326

4-Aminophenyl acetonitrile (Aldrich, 0.214 g, 1.62 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (7 mL) were used as in general procedure X. The product was purified by flash chromatography using

7:3 hexanes:ethyl acetate with 0.01% NEt_3 to afford **326** as an orange solid (0.26 g, 40%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4 (s, 2H), 4.7 (s, 2H), 7.2 (d, 1H), 7.3 (d, 2H), 7.45 (s, 1H), 7.5-7.6 (m, 4H), 7.65 (m, 2H), 7.8 (d, 2H), 9.9 (s, 1H); MS (ES$^-$) *m/z* 403 (M-H)$^-$.

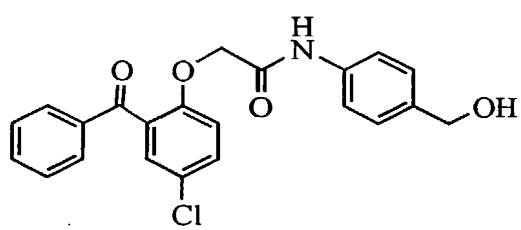
Example 133



327

Procaine (ICN, 0.382 g, 1.62 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.38 g, 1.24 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 24:1 methylene chloride:methanol to afford **327** as an off-white solid (0.037 g, 4.5%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1 (t, 6H), 2.8 (bs, 2H), 4.3 (bs, 2H), 4.8 (bs, 2H), 7.2 (d, 1H), 7.5-7.7 (m, 8H), 7.8 (d, 2H), 7.9 (d, 2H), 10.2 (s, 1H); MS (AP$^+$) *m/z* 509 (M+H)$^+$.

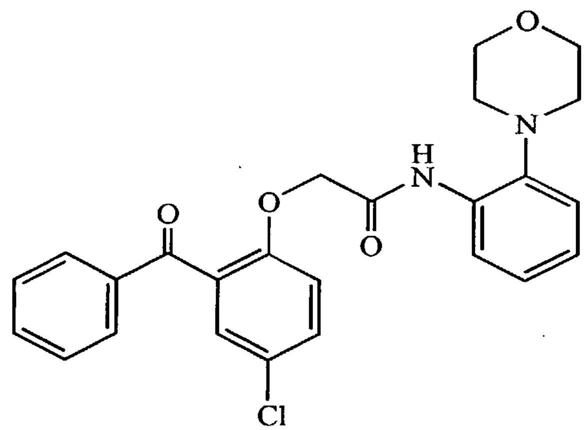
Example 134



328

4-Amino benzyl alcohol (Fluka, 0.2 g, 1.62 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 4:1 hexanes:ethyl acetate to afford **328** as a dark yellow solid (0.06 g, 10%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.45 (d, 2H), 4.7 (s, 2H), 5.1 (t, 1H), 7.2 (t, 3H), 7.45 (t, 3H), 7.55 (t, 2H), 7.6 (t, 2H), 7.8 (d, 2H), 9.7 (s, 1H); MS (ES$^-$) *m/z* 394 (M-H)$^-$.

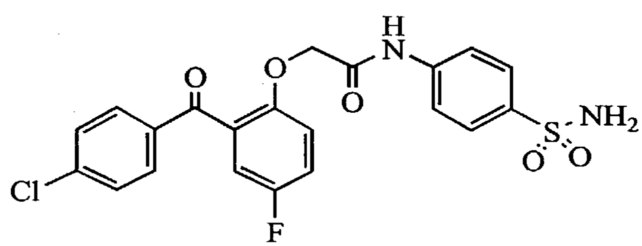
Example 135



329

2-Morpholinoaniline (Lancaster, 0.288 g, 1.62 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 9:1 and 4:1 hexanes:ethyl acetate to afford **329** as an off-white solid (0.082 g, 11%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.65 (s, 4H), 3.5 (s, 4H), 4.7 (s, 2H), 7.1 (t, 2H), 7.15 (s, 1H), 7.3 (d, 1H), 7.4 (t, 2H), 7.5 (m, 2H), 7.6 (d, 1H), 7.7 (d, 2H), 7.9 (s, 1H), 8.7 (s, 1H); MS (ES$^+$) *m/z* 451 $(M+H)^+$.

Example 136

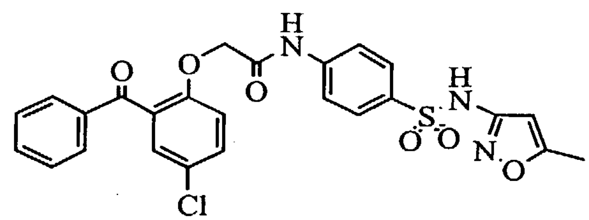


330

Sulfanilamide (Aldrich, 0.263 g, 1.53 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **323** (0.5 g, 1.53 mmol) in acetonitrile (5 mL) were used as in general procedure X. The reaction mixture was concentrated under reduced pressure, triturated with methylene chloride, ethyl acetate, hexanes, and methanol, and filtered. The resulting solid was washed with diethyl ether and ethyl acetate to give an off-white solid, which was triturated with water and filtered to give **330** as an off-white solid (0.078 g, 11%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.7 (s, 2H), 7.15 (dd, 1H), 7.2 (s, 2H), 7.25 (d,

1H), 7.35 (t, 1H), 7.5 (d, 2H), 7.65 (d, 2H), 9.87 (bs, 2H), 10.25 (s, 1H); MS (ES$^-$) *m/z* 461 (M-H)$^-$.

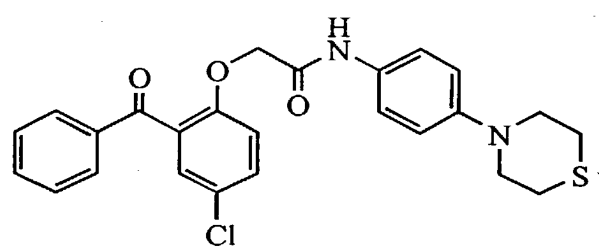
Example 137



331

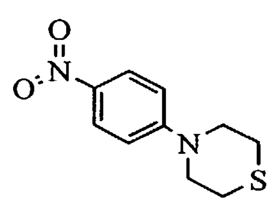
Sulfamethoxazole (Aldrich, 0.424 g, 1.67 mmol), NEt_3 (0.25 mL, 1.79 mmol), acetonitrile (5 mL), and acid chloride **320** (0.52 g, 1.68 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 3:2 hexanes:ethyl acetate as elutant to afford **331** as an off-white solid (0.021 g, 2.4%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.3 (s, 3H), 4.7 (s, 2H), 6.1 (s, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 7.45 (d, 2H), 7.55 (m, 2H), 7.7 (d, 2H), 7.8 (d, 4H), 10.3 (s, 1H), 11.3 (s, 1H); MS (ES$^-$) *m/z* 524 (M-H)$^-$.

Example 138



332

Step A:

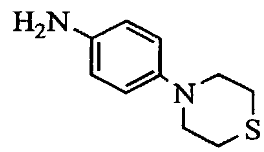


333

4-Nitro-bromobenzene (Aldrich, 10.31 g, 51 mmol) in pyridine (85 mL), sodium bicarbonate (7.5 g, 89 mmol), and water (3 mL) were used as in general procedure XI to

afford **333** as a yellow crystalline solid (6.5g, 57%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.6 (t, 4H), 3.8 (t, 4H), 7 (d, 2H), 8 (d, 2H); MS (ES$^+$) *m/z* 225 (M+H)$^+$.

Step B:



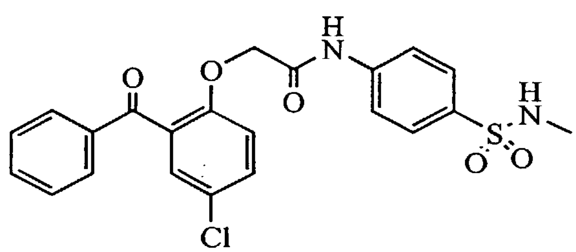
334

Compound **333** (1.04 g, 4.63 mmol), palladium on carbon (0.2 g, 10% w/w), ethanol (20 mL) and THF (20 mL) were used as in general procedure XII to afford **334** as a brown solid (0.95 g, crude material).

Step C:

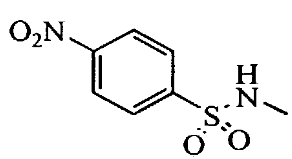
Compound **334** (0.95 g, 4.9 mmol), NEt_3 (1 mL, 7.2 mmol), acetonitrile, and acid chloride **320** (1.51 g, 4.9 mmol) in acetonitrile (20 mL total reaction volume) were used as in general procedure X without heat. The reaction mixture was filtered and washed with acetonitrile followed by diethyl ether to afford **332** as an off-white solid (1.154g, 51%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.6 (m, 4H), 3.4 (m, 4H), 4.6 (s, 2H), 6.9 (d, 2H), 7.15 (d, 1H), 7.3 (d, 2H), 7.4 (s, 1H), 7.5 (t, 2H), 7.55-65 (m, 2H), 7.8 (d, 2H), 9.45 (s, 1H); MS (ES$^-$) *m/z* 465 (M-H)$^-$.

<u>**Example 139**</u>



335

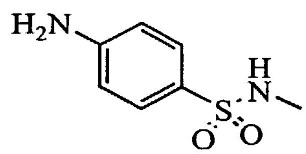
Step A:



336

4-Nitrobenzenesulfonylchloride (Aldrich, 44.3 g, 200 mmol) was added portionwise to a solution of methylamine in ethanol (250 mL, 208 mmol) which was stirred at 0 °C under nitrogen. After removing the ice bath, the reaction was stirred for 45 min. Water (250 mL) was added and the resulting product was filtered to afford **336** as a crystalline solid (37.6 g, 87%). The crude material was used without purification.

Step B:



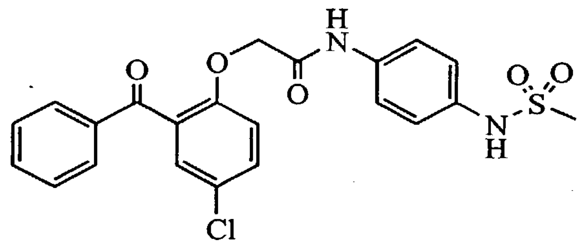
337

Palladium on carbon (2 g, 10% w/w) was added to a solution of compound **336** (17.3 g, 80 mmol), methanol (80 mL), THF (80 mL), and hydrochloric acid (concentrated, 7 mL, 84 mmol) and used as in general procedure XII to afford **337** as a white solid (14.3 g, 80%). The crude material was used without purification.

Step C:

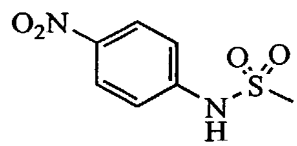
Compound **337** (0.32 g, 1.44 mmol), NEt_3 (0.5 mL, 3.6 mmol), acetonitrile (5 mL), and acid chloride **320** (0.444 g, 1.44 mmol) in acetonitrile (5 mL) were used as in general procedure X. After 6 d, another equivalent of acid chloride **320** (0.444 g, 1.44 mmol) was added and the solution was stirred. The reaction mixture was filtered and the resulting solid was washed with acetonitrile and water, and suspended in ethyl acetate. The suspension was filtered and the filtrate concentrated in vacuo to afford **335** as an off-white solid (0.152 g, 23%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.3 (d, 3H), 4.7 (s, 2H), 7.15 (d, 1H), 7.3 (m, 1H), 7.45 (s, 1H), 7.5 (t, 2H), 7.54-7.62 (m, 2H), 7.7 (s, 4H), 7.8 (d, 2H), 10.2 (s, 1H); MS (ES$^-$) *m/z* 457 (M-H)$^-$.

Example 140



338

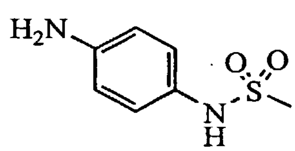
Step A:



339

Methanesulfonyl chloride (5 g, 43.9 mmol) was added dropwise to a solution of 4-nitroaniline (Aldrich, 5.95 g, 43.1 mmol) in dry pyridine (100 mL) which was stirred at –15°C under nitrogen. After storing the resulting solution at 0°C for 2 d, the solvent was removed in vacuo. The product was triturated with ice water, filtered, and washed with ice water to afford **339** as an orange/yellow solid (8.87 g, 95%). The crude product was used without purification.

Step B:



340

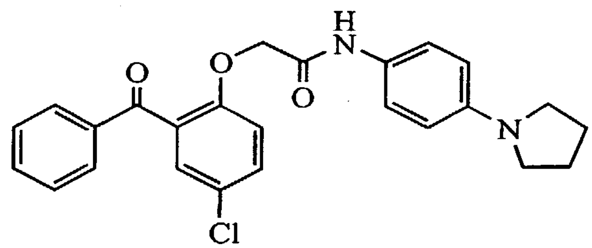
Palladium on carbon (0.14 g, 10% w/w) was added to a solution of compound **339** (1.0 g, 4.63 mmol), ethanol (15 mL), and THF (20 mL) and the resulting suspension was used as in general procedure XII with 50 psi of hydrogen to afford **340** as an orange oil (0.85 g). The crude material was used without purification.

Step C:

Compound **340** (0.85 g, 4.6mmol), NEt_3 (0.87 mL, 6.2 mmol), acetonitrile (8 mL), and acid chloride **320** (1.29 g, 4.2 mmol) in acetonitrile (8 mL) were used as in general procedure X. After 2 d, water was added and the resulting mixture was extracted with

ethyl acetate. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography using 35% ethyl acetate in hexanes to afford **338** as an off-white/ pale yellow solid (0.480 g, 23%). ^1H NMR (DMSO-d_6, 300 MHz) δ 2.95 (s, 3H), 4.7 (s, 2H), 7.15 (d, 2H), 7.2 (d, 1H), 7.45 (d, 3H), 7.7 (m, 7H), 7.85 (d, 2H), 9.6 (s, 1H), 9.8 (s, 1H); MS (ES$^-$) *m/z* 457 (M-H)$^-$.

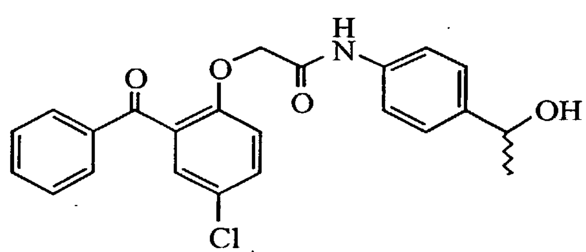
Example 141



341

4-(N-pyrrolidine)aniline (Apin, 0.262 g, 1.61 mmol), NEt_3 (0.23 mL, 1.65 mmol), acetonitrile (5 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 9:1 and 4:1 hexanes:ethyl acetate to afford **341** as an off-white solid (0.112 g, 16%). ^1H NMR (DMSO-d_6, 300 MHz) δ 2 (t, 4H), 3.2 (t, 4H), 4.66 (s, 2H), 6.5 (d, 2H), 7.2 (s, 1H), 7.3 (t, 2H), 7.45 (s, 1H), 7.5 (t, 2H), 7.6 (m, 2H), 7.8 (d, 2H), 9.3 (s, 1H); MS (ES$^-$) *m/z* 433 (M-H)$^-$.

Example 142



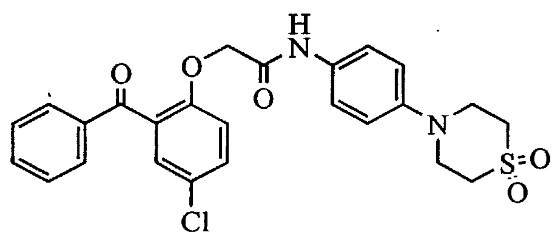
342

1-(4-Aminophenyl) ethanol (Apin, 0.25 g, 1.82 mmol), NEt_3 (0.25 mL, 1.79 mmol), acetonitrile (7 mL), and acid chloride **320** (0.51 g, 1.65 mmol) in acetonitrile (6 mL) were used as in general procedure X. The product was purified by flash chromatography using 45% ethyl acetate in hexanes to afford **342** as a colorless solid (0.428 g, 63%). ^1H NMR

(DMSO-d_6, 400 MHz) δ 1.25 (d, 3H), 4.6 (m, 1H), 4.7 (s, 2H), 5.1 (s, 1H), 7.2 (d, 1H), 7.25 (d, 2H), 7.4 (d, 3H), 7.5 (t, 2H), 7.6 (m, 2H), 7.8 (d, 2H), 9.7 (s, 1H); MS (ES^-) *m/z* 408 $(M-H)^-$.

The racemic mixture was separated to give 2 enantiomers using the following conditions: an OJ chiral column, 22% IPA, 2 mL/min., 26°C, 3000 psi on SFC. Enantiomer 1 eluted at 9.214 min. to give an off-white solid **342-A** (0.092 g, 14%). Enantiomer 2 eluted at 11.118 min. to give another off-white solid **342-B** (0.059 g, 9%). The enantiomeric purity was found to be >99% and the absolute stereochemistry were not determined.

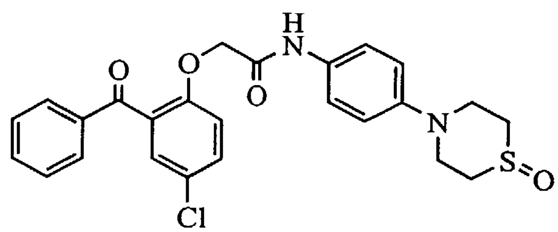
Example 143



343

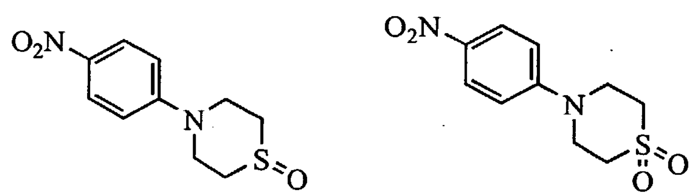
3-Chloroperoxybenzoic acid (~60%, 0.54 g, 1.9 mmol) was added portionwise to a solution of compound **332** (0.4 g, 0.86 mmol) in methylene chloride (30 mL) and stirred at rt. After 4 days, filtered the suspension and washed the solids with methylene chloride. The filtrate was washed with saturated sodium meta bisulfite, 10% NaOH, and water. The organics were dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography using 99:1 methylene chloride:methanol and further purified by TLC prep plate eluted with 99:1 methylene chloride:methanol to afford **343** as an off-white foam (0.062 g, 14%). ^{1}H NMR ($CDCl_3$, 300 MHz), δ 3.1 (t, 4H), 3.8 (t, 4H), 4.7 (s, 2H), 6.9 (d, 2H), 7.05 (d, 1H), 7.4 (s, 1H), 7.5-7.6 (m, 5H), 7.65 (t, 1H), 7.9 (d, 2H), 9.05 (s, 1H); MS (AP^-) *m/z* 497 $(M-H)^-$.

Example 144



344

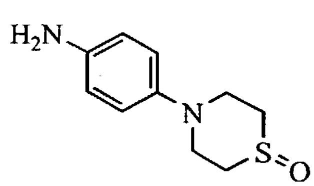
Step A:



345 **346**

3-Chloroperoxybenzoic acid (~60%, 20.3 g, 70.6 mmol) in methylene chloride was added dropwise to a cooled solution of compound **333** (11.5 g, 51.1 mmol) in methylene chloride (250 mL total reaction volume) and stirred at –78 °C. After 2 h, the reaction was warmed to rt and stirred overnight. The reaction mixture was washed with saturated sodium meta bisulfite, 2N NaOH, and water. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to give a mixture of **345** and **346** as a yellow solid (8.47 g, crude material). The crude material was used without purification.

Step B:



347

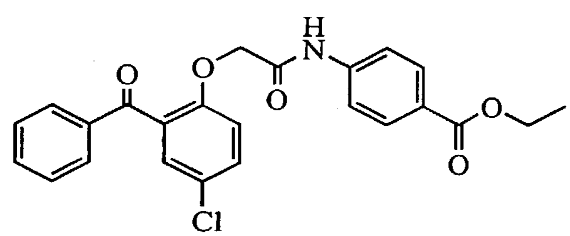
The mixture of **345** and **346** (8.47 g, 35.3 mmol), palladium on carbon (1.4 g, 10% w/w), ethanol (100 mL) and THF (50 mL) were used as in general procedure XII using 60 psi of hydrogen. The product was purified by flash chromatography using a gradient between 4:1 and 9:2 hexanes:ethyl acetate to afford **347** as a yellow solid (3.94 g, 53.2 %). ^1H

NMR (DMSO-d_6, 400 MHz) δ 2.7 (dd, 2H), 2.9 (m, 2H), 3.16 (dd, 2H), 3.7 (t, 2H), 4.6 (bs, 2H), 6.46 (dd, 2H), 6.71 (dd, 2H); MS (ES^+) m/z 211 $(M+H)^+$.

Step C:

Carboxylic acid **105** (4.15 g, 14.3 mmol), HCA (1.08 mL, 7.1 mmol), THF (60 mL), PPh_3 (1.82 g, 6.95 mmol) in THF (15 mL), sulfoxide **347** (3 g, 14.3 mmol) in THF (125 mL), and pyridine (15 mL, 185 mmol) were used as in general procedure XIII. The product was purified by flash chromatography using a gradient between 99:1 and 9:1 methylene chloride:methanol and further purified by triturating the resulting solid with methanol and ethanol, filtering, and washing the solids with water and methanol to afford **344** as a tan solid (2.7g, 39%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.7 (d, 2H), 2.9 (t, 2H), 3.5 (d, (2H), 3.7 (t, 2H), 4.7 (s, 2H), 7 (d, 2H), 7.2 (d, 1H), 7.4 (d, 2H), 7.47 (s, 1H), 7.55 (d, 2H), 7.65 (t, 2H), 7.8 (d, 2H), 9.6 (s, 1H); MS (AP^-) m/z 481 $(M-H)^-$.

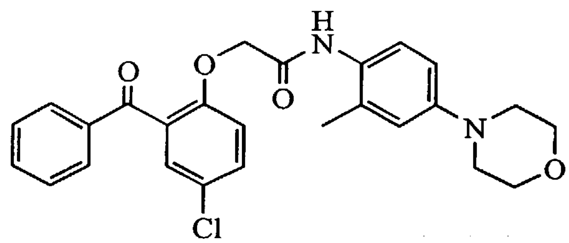
__Example 145__



348

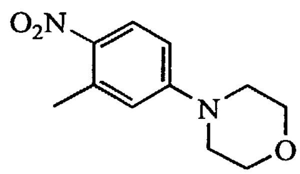
Glycerol-p-aminobenzoate (ICN, 0.342 g, 1.62 mmol), NEt_3 (0.25 mL, 1.79 mmol), acetonitrile (7 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (8 mL) were used as in general procedure X. The product was purified by flash chromatography using 9:1 hexanes:ethyl acetate then further purified by flash chromatography using 99:1 methylene chloride:methanol to afford **348** as an off-white solid (0.02 g, 3%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.3 (t, 3H), 4.3 (q, 2H), 4.8 (s, 2H), 7.5 (d, 1H), 7.6 (d, 2H), 7.7 (d, 4H), 7.8 (d, 2H), 7.9 (d, 2H), 10.2 (s, 1H); MS (ES^-) m/z 436 $(M-H)^-$.

__Example 146__



349

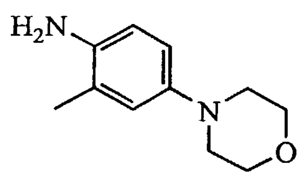
Step A:



350

4-Chloro-2-nitrotoluene (SALOR, 2 g, 11.7 mmol) in pyridine (25 mL), sodium bicarbonate (2 g, 23.8 mmol), water (5 mL), and morpholine (Aldrich, 2.03 g, 23.3 mmol) were used as in general procedure XI to afford **350** as a yellow solid (0.804 g, 31%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.5 (s, 3H), 3.4 (t, 4H), 3.7 (t, 4H), 6.9 (d, 2H), 8 (d, 1H). The crude material was used without purification.

Step B:



351

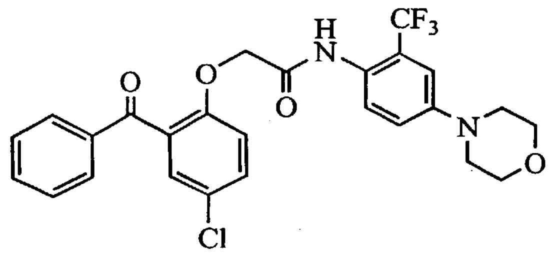
Compound **350** (0.72 g, 4.63 mmol), palladium on carbon (0.1 g, 10% w/w), ethanol (20 mL), and THF (20 mL) were used as in general procedure XII using 50 psi of hydrogen to afford **351** as a brown solid (0.623 g, crude material).

Step C:

Compound **351** (0.623 g, 3.2 mmol), NEt_3 (1.3 mL, 9.3 mmol) in acetonitrile (8 mL), and acid chloride **320** (1.02 g, 3.3 mmol) in acetonitrile (7 mL) were used as in general procedure X. The product was purified by flash chromatography using 99.5:0.5 methylene chloride:methanol to afford **349** as an orange foam (0.072 g, 5%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.9 (s, 3H), 3 (t, 4H), 3.7 (t, 4H), 4.65 (s, 2H), 6.7 (d, 1H), 6.73 (s, 1H), 7.1

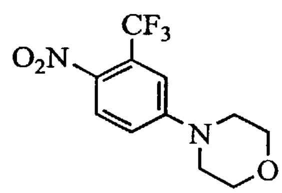
(d, 1H), 7.2 (d, 1H), 7.4 (s, 1H), 7.5 (t, 2H), 7.6 (t, 2H), 7.75 (d, 2H), 8.8 (s, 1H); MS (ES^-) *m/z* 463 $(M-H)^-$.

Example 147



352

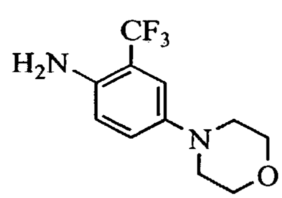
Step A:



353

5-Bromo-2-nitrobenzotrifluoride (Lancaster, 2 g, 7.4 mmol) in pyridine (20 mL), sodium bicarbonate (1.25 g, 14.8 mmol), water (5 drops), and morpholine (Aldrich, 1.29 g, 14.8 mmol) were used as in general procedure XI to afford **353** as a yellow solid (1.62 g, 79%). ^1H NMR (DMSO-d_6, 400 MHz) δ 3.5 (t, 4H), 3.8 (t, 4H), 7.25 (d, 1H), 7.3 (s, 1H), 8.1 (d, 1H). The crude product was used without purification.

Step B:



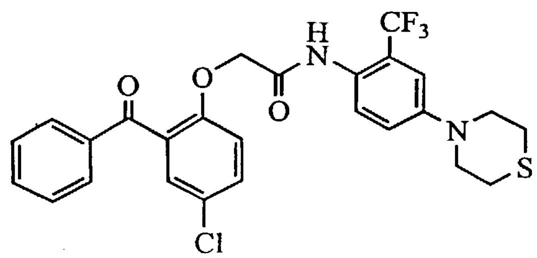
354

Compound **353** (1.62 g, 5.9 mmol), palladium on carbon (0.2 g, 10% w/w), ethanol (12 mL) and THF (12 mL) were used as in general procedure XII using 75 psi of hydrogen to afford **354** as a brown solid (1.41 g, crude material).

Step C:

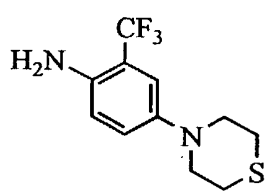
Compound **354** (1.41 g, 5.73 mmol), NEt_3 (0.8 mL, 5.74 mmol), acetonitrile (15 mL), and acid chloride **320** (1.8 g, 5.82 mmol) in acetonitrile (15 mL) were used as in general procedure X. The product was purified by flash chromatography using 35% ethyl acetate in hexanes and further purified by flash chromatography using 1:1 ethyl acetate:hexanes to afford **352** as an off-white solid (0.426 g, 14%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.2 (t, 4H), 3.75 (t, 4H), 4.7 (s, 2H), 7.15 (s, 1H), 7.2 (m, 3H), 7.45-7.55 (m, 3H), 7.6 (t, 2H), 7.8 (d, 2H), 9 (s, 1H); MS (ES$^-$) m/z 517 (M-H)$^-$.

Example 148



355

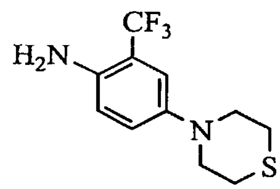
Step A:



356

5-Bromo-2-nitrobenzotrifluoride (Lancaster, 2 g, 7.4 mmol) in pyridine (20 mL), sodium bicarbonate (1.25 g, 14.9 mmol), water (5 drops), and thiomorpholine (Aldrich, 1.52 g, 14.7 mmol) were used as in general procedure XI to afford **356** as a yellow solid (1.63 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.65 (t, 4H), 3.88 (t, 4H), 7.2 (d, 1H), 7.22 (s, 1H), 8 (d, 1H).

Step B:



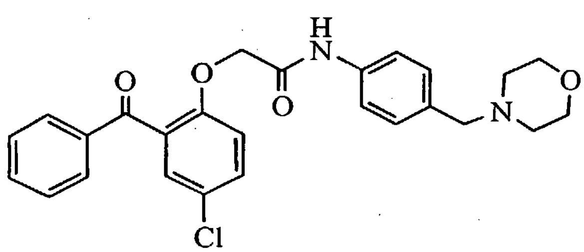
357

Compound **356** (1.63 g, 5.6 mmol), palladium on carbon (0.3 g, 10% w/w), ethanol (12 mL) and THF (12 mL) were used as described in general procedure XII using 75 psi of hydrogen to afford **357** as a brown oil (1.29 g, 88%). The crude material was used without purification.

Step C:

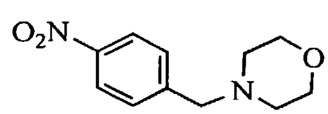
Compound **357** (1.29 g, 4.92 mmol), NEt_3 (0.7 mL, 5.02 mmol), acetonitrile (15 mL), and acid chloride **320** (1.52 g, 4.92 mmol) in acetonitrile (15 mL) were used as in general procedure X. The product was purified by flash chromatography using 35% ethyl acetate in hexanes to afford **355** as an orange oil (0.264 g, 10%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.62 (m, 4H), 3.57 (m, 4H), 4.68 (s, 2H), 7.07 (d, 1H), 7.16 (q, 3H), 7.41 (d, 1H), 7.45 (m, 3H), 7.58 (m, 2H), 7.75 (d, 2H), 9 (s, 1H); MS (ES^-) *m/z* 533 $(M-H)^-$.

Example 149



358

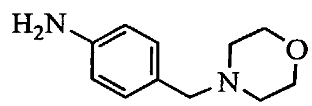
Step A:



359

Morpholine (Aldrich, 0.74 mL, 8.5 mmol) was added dropwise to a solution of 4-nitro-benzylbromide (Aldrich, 2 g, 9.26 mmol), in acetone (20 mL), and potassium carbonate (2.4 g, 17.4 mmol). The resulting suspension was stirred at rt for 6 d under nitrogen. The mixture was filtered and the filtrate was concentrated in vacuo to afford **359** as a pale yellow solid (1.89 g, crude material).

Step B:



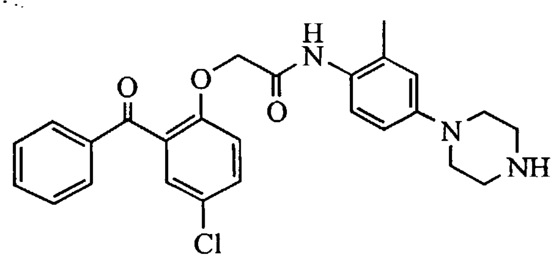
360

Compound **359** (1.89 g, 4.63 mmol), palladium on carbon (0.325 g, 10% w/w), ethanol (25 mL) and THF (25 mL) were used as in general procedure XII using 50 psi of hydrogen to afford **360** as a brown solid (1.6 g, crude material).

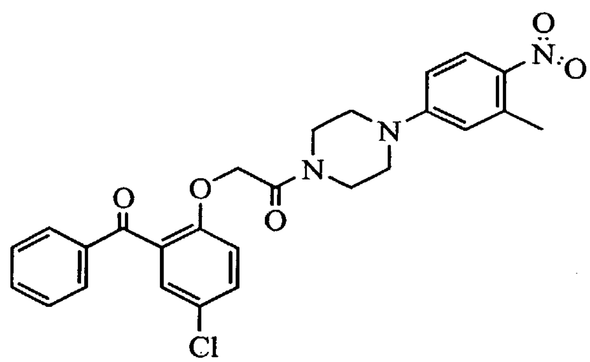
Step C:

Compound **360** (1.6 g, 8.3 mmol), NEt_3 (0.95 mL, 6.8 mmol), acetonitrile (7 mL), and acid chloride **320** (1.53 g, 4.95 mmol) in acetonitrile (7 mL) were used as in general procedure X. The product was purified by flash chromatography using a gradient between 9:1 and 4:1 hexanes:ethyl acetate **358** as an off-white solid (0.264g, 12%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.35 (d, 4H), 3.41 (s, 3H), 3.57 (t, 4H), 4.73 (s, 2H), 7.23 m, 3H), 7.47-7.67 (m, 7H), 7.83 (d, 2H), 9.78 (s, 1H); MS (ES$^-$) *m/z* 463 (M-H)$^-$.

<u>**Example 150 and Example 151**</u>

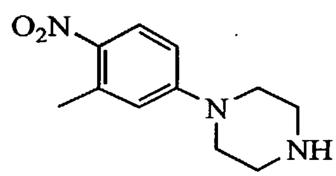


361



362

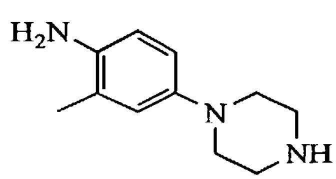
Step A:



363

4-Chloro-2-nitrotoluene (SALOR, 1.46 g, 8.5 mmol) in pyridine (5 mL) was added dropwise to a solution of pyridine (22 mL), sodium bicarbonate (0.73 g, 8.7 mmol), piperazine (Aldrich, 1.5 g, 17.4 mmol), and water (3 mL) and the resulting mixture was refluxed for 2 d under nitrogen. Additional piperazine (1.5 g, 17.4 mmol) and sodium bicarbonate (0.73 g, 8.7 mmol) were added and the mixture was refluxed overnight. Acetone (200 mL) was added to the mixture and it was filtered hot. Water was added to the filtrate and the mixture was cooled to rt. Filtered the resulting suspension and concentrated the filtrate in vacuo. The concentrate was dissolved in hot methanol and ether and cooled to rt. The resulting mixture was filtered and the filtrate was concentrated in vacuo to afford **363** as a yellow solid (4.22 g). MS (ES^+) *m/z* 222 $(M+H)^+$. The crude product was used without purification.

Step B:



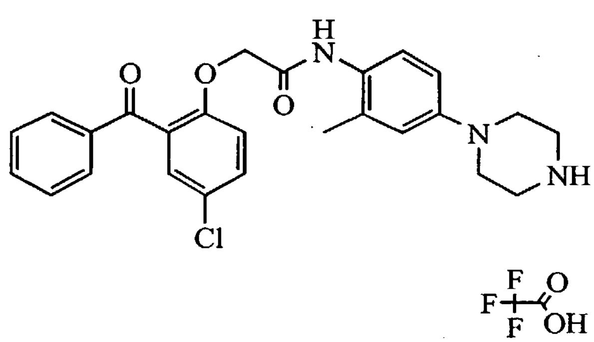
364

Compound **363** (1.88 g, 8.5 mmol), palladium on carbon (0.563 g, 10% w/w), ethanol (35 mL), and THF (35 mL) were used as in general procedure XII to afford **364** as a yellow oil (1.7 g). The crude product was used without purification.

Step C:

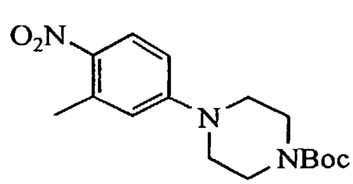
Compound **364** (1.7 g, 8.9 mmol), NEt_3 (1.4 mL, 10 mmol), acetonitrile (12 mL), and acid chloride **320** (2.36 g, 7.6 mmol) in acetonitrile (12 mL) were used as in general procedure X. Water was added to the reaction mixture and the resulting suspension was filtered. The filtrate was partitioned between 2N NaOH and ethyl acetate. The aqueous layer was acidified with 1N sodium hydrogen sulfate to pH 1 and extracted with ethyl acetate. The product was purified by flash chromatography using a gradient between 3:2 hexanes:ethyl acetate, ethyl acetate, and methanol to afford **362** as a yellow solid (0.250 g) MS (ES^+) *m/z* 494 $(M+H)^+$ and **361** as an orange solid (0.005g, 0.1%). ^1H NMR (DMSO-d_6, 400 MHz) δ 1.96 (s, 3H), 2.79 (m, 4H), 2.97 (m, 4H), 4.66 (s, 2H), 6.66 (m, 2H), 7.05 (d, 1H), 7.2 (d, 1H), 7.42 (d, 1H), 7.46 (t, 2H), 7.6 (t, 2H), 7.75 (d, 2H), 8.79 (s, 1H); MS (ES^+) *m/z* 464 $(M+H)^+$.

Example 152



365

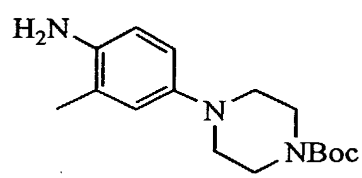
Step A:



366

5-Fluoro-2-nitrotoluene (Aldrich, 2 g, 12.9 mmol) in pyridine (5 mL) was added dropwise to a solution of pyridine (15 mL), sodium bicarbonate (1.62 g, 19.3 mmol), 1-t-butoxycarbonyl piperazine (Aldrich, 3.6 g, 19.3 mmol), and water (1.2 mL) and the resulting mixture was refluxed overnight. Acetone was added to the reaction and the resulting mixture was filtered hot. Water was added and the mixture was cooled to rt. The resulting solid was filtered and washed with water and ether to afford **366** as an orange solid (4.02 g). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.39 (s, 9H), 2.47 (s, 3H), 3.41 (s, 8H), 6.84 (m, 2H), 7.97 (d, 1H). The crude material was used without purification.

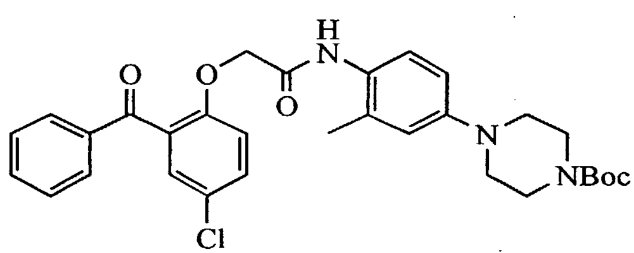
Step B:



367

Compound **366** (4.02 g, 12.5 mmol), palladium on carbon (1.2 g, 10% w/w), ethanol (90 mL) and THF (10 mL) were used as in general procedure XII using 80 psi of hydrogen. The product was filtered through a celite pad eluted with 9:1 methylene chloride:methanol and concentrated in vacuo to afford **367** as a pink solid (2.926 g, crude material).

Step C:



368

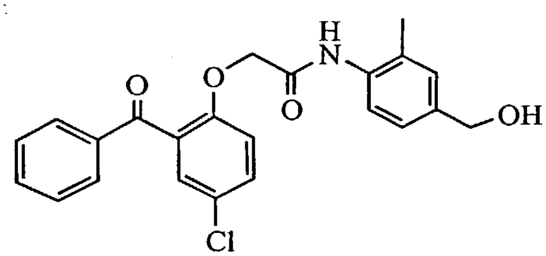
Acid chloride **320** in methylene chloride was added dropwise to a solution of compound **367** (0.362 g, 1.24 mmol) in pyridine (20 mL) and stirred for 2 days. The reaction was concentrated in vacuo, ethanol and ice were added, and the resulting solid was filtered and washed with ether to afford **368** as a yellow solid (0.118 g, 20.2%). ^{1}H NMR (DMSO-d_6,

400 MHz) δ 1.38 (d, 9H), 1.95 (s, 3H), 3 (d, 4H), 3.4 (s, 4H), 4.67 (s, 2H), 6.7 (m, 2H), 7.1 (d, 1H), 7.42 (d, 1H), 7.48 (m, 2H), 7.6 (m, 2H), 7.75 (d, 2H), 8.8 (s, 1H).

Step D:

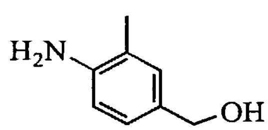
TFA (15 mL, 195 mmol) was added to a solution of compound **368** (0.118 g, 0.21 mmol) in acetonitrile and stirred overnight. The reaction mixture was concentrated in vacuo after carbon tetrachloride was added to azeotrope off the TFA. This procedure was repeated multiple times. The mixture was concentrated in vacuo to afford **365** as a yellow solid (0.085 g, 88%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.96 (s, 3H), 3.08 (d, 4H), 3.17 (d, 4H), 4.67 (s, 2H), 6.72 (m, 2H), 7.1 (d, 1H), 7.2 (d, 1H), 7.42 (s, 1H), 7.46 (m, 2H), 7.6 (m, 2H), 7.75 (d, 2H), 8 (bs, 1H), 8.86 (s, 1H); MS (ES$^+$) *m/z* 464 (M+H)$^+$.

__Example 153__



369

Step A:



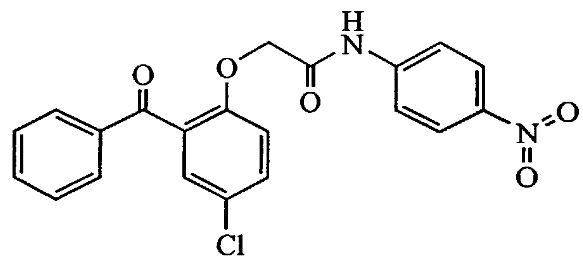
370

3-Methyl-4-nitrobenzyl alcohol (Aldrich, 1g, 5.98 mmol), palladium on carbon (0.265 g, 10% w/w), ethanol (12 mL), and THF (12 mL) were used as in general procedure XII using 58 psi hydrogen to afford **370** as a yellow oil (0.65 g, 79%). The crude material was used without purification.

Step B:

Compound **370** (0.65 g, 4.74 mmol), NEt_3 (0.95 mL, 6.82 mmol), acetonitrile (10 mL), and acid chloride **320** (0.5 g, 1.62 mmol) in acetonitrile (10 mL) were used as in general procedure X. The product was purified by flash chromatography using 1:1 hexanes:ethyl acetate to afford **369** as a yellow solid (0.041 g, 2.1%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2 (s, 3H), 4.4 (s, 2H), 4.7 (s, 2H), 5.1 (bs, 1H), 7.1 (m, 2H), 7.25 (m, 2H), 7.45 (m, 3H), 7.6 (m, 2H), 7.76 (d, 2H), 8.9 (s, 1H); MS (ES$^-$) *m/z* 408 (M-H)$^-$.

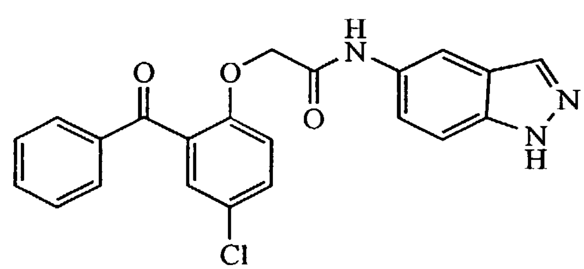
__Example 154__



371

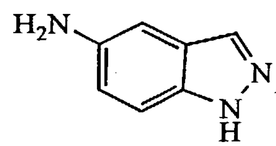
4-Nitroaniline (Sigma, 0.244 g, 1.77 mmol), NEt_3 (0.25 mL, 1.79 mmol), acetonitrile (5 mL), and acid chloride **320** (0.54 g, 1.75 mmol) in acetonitrile (5 mL) were used as in general procedure X. The product was purified by flash chromatography using 4:1 hexanes:ethyl acetate to afford **371** as an off-white solid (0.012 g, 2%). ^1H NMR ($CDCl_3$, 300 MHz) δ 4.8 (s, 2H), 7.05 (d, 1H), 7.4 (d, 1H), 7.5 (m, 3H), 7.65 (t, 1H), 7.9 (d, 2H), 8 (d, 2H), 8.25 (d, 2H), 10 (s, 1H); MS (ES$^-$) *m/z* 409 (M-H)$^-$.

__Example 155__



372

Step A:



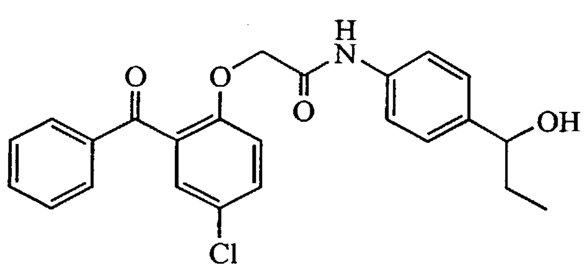
373

5-Nitroindazole (Aldrich, 1.2 g, 7.36 mmol), palladium on carbon (0.23 g, 10% w/w), ethanol (25 mL), and THF (5 mL) were used as in general procedure XII using 78 psi of hydrogen to afford **373** as a pink solid (0.98 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.7 (s, 2H), 6.7 (dd, 2H), 7.2 (d, 1H), 7.7 (s, 1H), 12.5 (s, 1H).

Step B:

Compound **373** (1 g, 7 mmol), NEt_3 (1.2 mL, 8.6 mmol), acetonitrile (20 mL), and acid chloride **320** (1.9 g, 6.2 mmol) in acetonitrile (10 mL) were used as in general procedure X. Ice water was added and the resulting suspension was filtered, washed with water, and the solid was recrystallized from ethanol and water. The resulting precipitate was filtered and washed with ether to afford **372** as a pink solid (0.679 g, 17.3%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.7 (s, 2H), 7.2 (d, 1H), 7.3 (d, 1H), 7.4-7.5 (m, 4H), 7.55-7.6 (m, 2H), 7.6 (dd, 2H), 8 (s, 2H), 9.7 (s, 1H), 13 (s, 1H); MS (ES$^-$) *m/z* 406 (M-H)$^-$.

__Example 156__

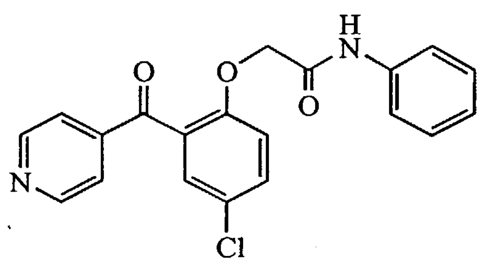


374

4-Aminophenyl ethyl carbinol (Apin, 0.254 g, 1.7 mmol), NEt_3 (0.28 mL, 2 mmol), acetonitrile (6 mL), and acid chloride **320** (0.53 g, 1.7 mmol) in acetonitrile (6 mL) were used as in general procedure X. The mixture was filtered, washed with 1M sodium hydrogen sulfate, and the filtrate was extracted with ethyl acetate. The organics were

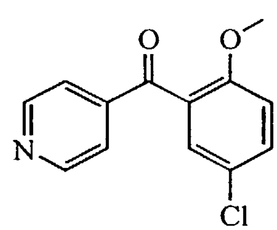
separated, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography using 93:7 methylene chloride:methanol, flash chromatography using 95:5 methylene chloride:methanol, a TLC prep plate using 92:8 methylene chloride:methanol, and a TLC prep plate using 9:1 methylene chloride:methanol to afford **374** as an off-white solid (0.029 g, 4%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.8 (t, 3H), 1.6 (m, 2H), 4.4 (m, 1H), 4.7 (s, 2H), 5.08 (d, 1H), 7.2 (t, 3H), 7.47 (d, 3H), 7.55 (m, 2H), 7.65 (m, 2H), 7.85 (d, 2H), 9.7 (s, 1H); MS (ES$^-$) *m/z* 422 (M-H)$^-$.

Example 157

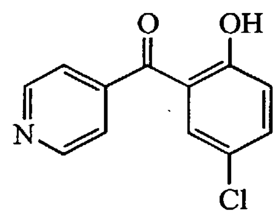


375

Compound **378** (0.143 g, 0.64 mmol) was added to a solution of compound **377** (0.15 g, 0.64 mmol), potassium carbonate (0.09 g, 0.65 mmol), and DMF (5 mL) and stirred overnight. The mixture was poured into ice water, filtered, and the resulting solid was washed with ether. The product was purified by TLC prep plate using 23:1 methylene chloride:methanol to afford **375** as an orange solid (0.021g, 9%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.7 (s, 2H), 7.06 (t, 1H), 7.25 (d, 1H), 7.3 (t, 2H), 7.55 (d, 2H), 7.58 (s, 1H), 7.67 (m, 3H), 8.77 (d, 2H) 9.86 (s, 1H); MS (ES$^-$) *m/z* 366 (M-H)$^-$.

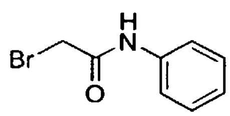


376



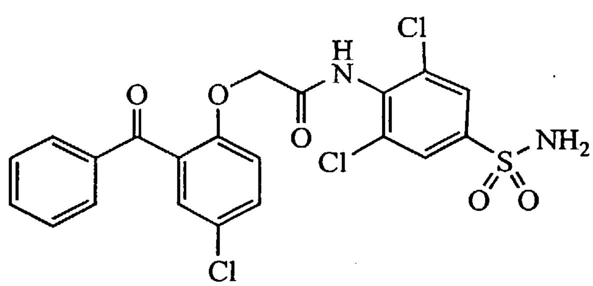
377

Compound **376** (4.2g, 17 mmol) in methylene chloride (100 mL), THF (100 mL), and BBr_3 (17g, 68 mmol) in methylene chloride (68 mL) were used as in general procedure IX to afford, after recrystallization from methanol, **377** as a yellow solid (1.1g, 28%). ^1H NMR (DMSO-d_6, 300 MHz) δ 7 (d, 1H), 7.6 (d, 2H), 8.2 (d, 2H), 9.7 (bs, 2H), 10.95 (s, 1H); MS (ES$^-$) *m/z* 232 (M-H)$^-$.



378

<u>Example 158</u>

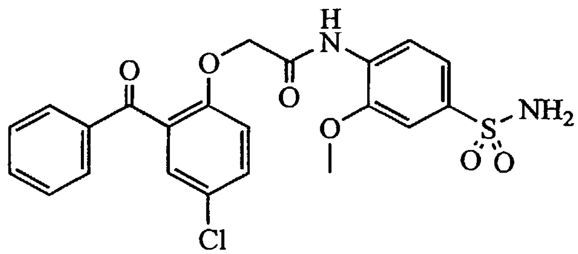


379

3,5-Dichloro sulfanilamide (Lancaster, 0.5 g, 2.1 mmol), NEt_3 (0.25 mL, 1.8 mmol), acetonitrile (10 mL), and acid chloride **320** (0.52 g, 1.7 mmol) in acetonitrile (6 mL) were used as in general procedure X. The reaction was heated to 40 °C and stirred for 3 d. Additional acid chloride **320** (0.52 g, 1.7 mmol) was added and the reaction was stirred for 7 d. The mixture was concentrated in vacuo, suspended in methylene chloride, filtered, and the filtrate was concentrated in vacuo. The product was purified by flash chromatography using 99:1 methylene chloride:methanol, by flash chromatography in a gradient between 1:1 and 9:1 ethyl acetate:hexanes, and by TLC prep plate using 23:1 methylene chloride:methanol, 7:3 ethyl acetate:hexanes, and 98:2 methylene chloride:methanol as elutant to afford **379** as an orange oil (0.038 g, 4.3%). ^1H NMR

(DMSO-d_6, 300 MHz) δ 4.56 (s, 2H), 6.57 (bs, 2H), 6.94 (d, 1H), 7.36 (s, 1H), 7.4 (m, 3H), 7.55 (m, 3H), 7.7 (d, 2H), 12.15 (bs, 1H); MS (ES$^-$) *m/z* 512 (M-H)$^-$.

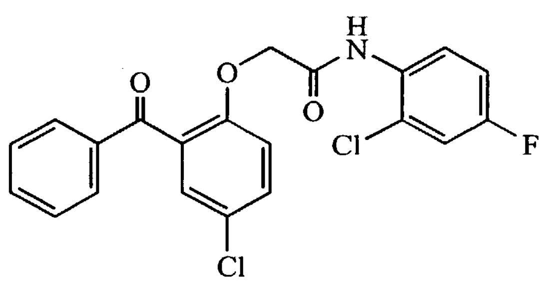
Example 159



380

3-Methoxy-4-amino sulfanilamide (Pfaltz Bauer, 0.5 g, 2.5 mmol), acetonitrile (16 mL), Et_3N (0.41 mL, 2.9 mmol), and acid chloride **320** (0.76 g, 2.5 mmol) in acetonitrile were used as in general procedure X. The reaction mixture was filtered and the resulting solids were washed with acetonitrile and ether to afford **380** as an off-white solid (0.169 g, 14.4 %). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.8 (s, 3H), 4.8 (s, 2H), 7.15 (d, 1H), 7.22 (d, 3H), 7.48 (m, 4H), 7.58 (d, 2H), 7.78 (d, 2H), 8.5 (s, 1H), 8.9 (s, 1H); MS (ES$^+$) *m/z* 575 (M+H)$^+$.

Example 160

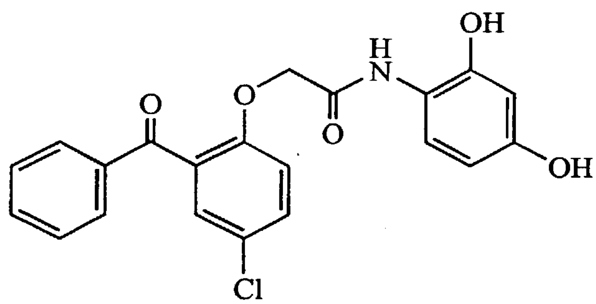


381

Acid chloride **320** (0.68 g, 2.2 mmol) in methylene chloride (5 mL) was added to a solution of 2-chloro-4-fluoroaniline (Aldrich, 0.5 g, 3.4 mmol), pyridine (12 mL) and the mixture was stirred overnight. The reaction mixture was poured over ice, ethanol (30 mL) was added, and the precipitate was filtered and washed with 1:1 ethanol:water and diethyl ether to afford **381** as a white solid (0.367 g, 40%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.8

(s, 2H), 7.25 (m, 2H), 7.5 (m, 9H), 7.65 (t, 2H), 7.75 (m, 1H), 7.8 (d, 2H), 9.2 (s, 1H); MS (ES^+) *m/z* 419 $(M+H)^+$.

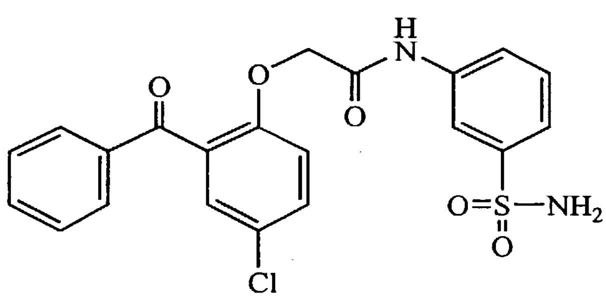
Example 161



382

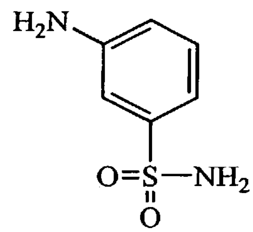
Resorcinol hydrochloride (Aldrich, 0.5 g, 3.4 mmol), acetonitrile (20 mL total reaction volume), Et_3N (0.75 mL, 5.4 mmol), and acid chloride **320** (0.8 g, 2.6 mmol) in acetonitrile were used as in general procedure X. The reaction mixture was poured over ice water and ethanol was added to the solution. The mixture was recrystallized from ethanol and water and the resulting solids were filtered and washed with ether to afford **382** as a pink solid (0.207 g, 20%). ^1H NMR (DMSO-d_6, 400 MHz) δ 4.6 (s, 2H), 6.1 (d, 1H), 6.28 (s, 1H), 7.19 (d, 1H), 7.4 (m, 4H), 7.56 (t, 2H), 7.75 (d, 2H), 8.5 (s, 1H), 9.1 (s, 1H), 9.6 (s, 1H); MS (ES^+) *m/z* 398 $(M+H)^+$.

Example 162



383

Step A:



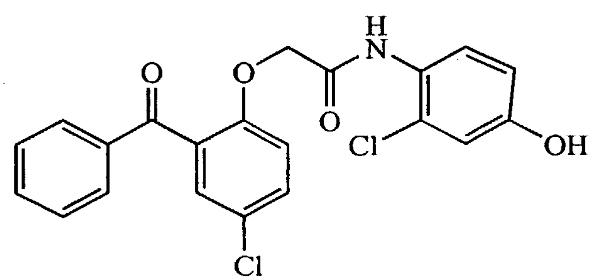
384

3-nitrobenzene sufonamide (5 g, 24.7 mmol), palladium on carbon (1 g, 10% w/w), methanol (75 mL), and THF (25 mL) were used as in general procedure XII using 67 psi of hydrogen to afford **384** as a solid (4.2 g). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.48 (bs, 2H), 6.67 (dd, 1H), 6.88 (d, 1H), 6.97 (t, 1H), 7.12 (t, 3H); MS (AP$^+$) *m/z* 173 $(M+H)^+$.

Step B:

Carboxylic acid **105** (0.29 g, 1 mmol), HCA (0.132 mL, 0.5 mmol), THF, PPh_3 (0.26 g, 1 mmol) in THF, metanilamide **384** (0.17 g, 1 mmol) in THF (4.5 mL total reaction volume), and pyridine (0.5 mL, 6.2 mmol) were used as in general procedure XIII. The reaction was concentrated in vacuo and the resulting solid was recrystallized from ethanol and water, filtered, and washed with ether to afford **383** as an off-white solid (0.207 g, 47%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.7 (s, 2H), 7.15 (d, 1H), 7.36 (s, 2H), 7.4-7.5 (m, 5H), 7.58 (m, 3H), 7.77 (d, 2H), 8.1 (s, 1H), 10.1 (s, 1H); MS (ES$^+$) *m/z* 445 $(M+H)^+$.

Example 163

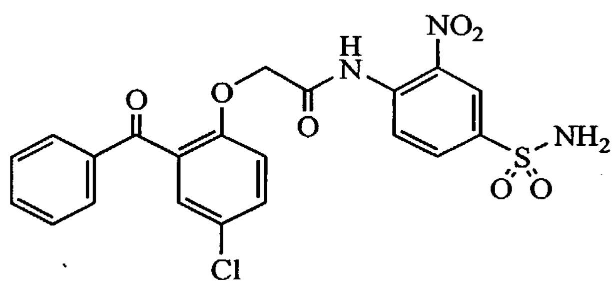


385

Carboxylic acid **105** (0.29 g, 1 mmol), HCA (0.08 mL, 0.53 mmol), methylene chloride (5 mL total reaction volume), and PPh_3 (0.26 g, 1 mmol) were combined in a round-bottom flask under nitrogen at -78°C. 4-Amino-3-chlorophenol (Aldrich, 0.145 g, 1 mmol) was free-based by partitioning it between methylene chloride and saturated sodium bicarbonate. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo

to give a pink solid that was dissolved in methylene chloride and Et_3N (0.26 mL, 1.9 mmol) and added dropwise to the reaction mixture at -78°C. The reaction was warmed to rt and concentrated in vacuo. The product was purified by flash chromatography using 4:1 hexanes:ethyl acetate to afford **385** as an orange solid (0.120 g, 29%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.7 (s, 2H), 6.67 (d, 1H), 6.79 (s, 1H), 7.2 (d, 1H), 7.35 (d, 1H), 7.4 (s, 1H), 7.5 (m, 2H), 7.6 (m, 2H), 7.75 (d, 2H), 8.9 (s, 1H), 9.8 (s, 1H); MS (ES$^+$) *m/z* 417 $(M+H)^+$.

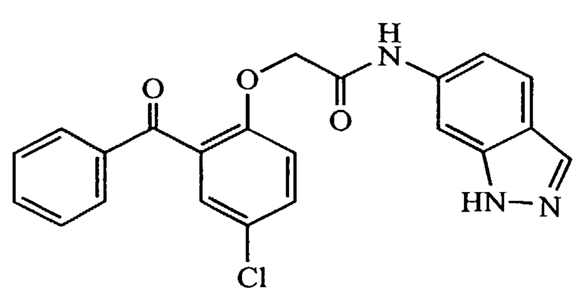
Example 164



386

Carboxylic acid **105** (0.67 g, 2.3 mmol), HCA (0.17 mL, 1.1 mmol), THF, PPh_3 (0.61 g, 2.3 mmol) in THF, 2-nitro-4-sulfanilamide (0.5 g, 2.3 mmol) in THF (20 mL total reaction volume), and pyridine (2.25 mL, 28 mmol) were used as in general procedure XIII. The reaction mixture was concentrated in vacuo and the product was purified by flash chromatography using a gradient between 9:1 hexanes:ethyl acetate and ethyl acetate to afford **386** as an off-white solid MS (ES$^-$) *m/z* 488 $(M-H)^-$.

Example 165

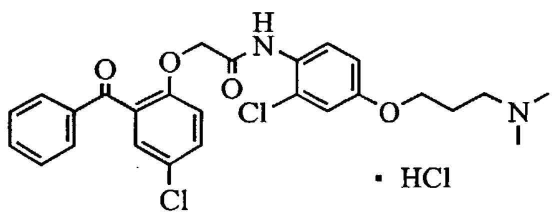


387

Carboxylic acid **105** (0.58 g, 2 mmol), HCA (0.152 mL, 1 mmol), THF, PPh_3 (0.52 g, 2 mmol) in THF, 6-aminoindazole (Aldrich, 0.26 g, 2 mmol) in THF (20 mL total reaction

volume), and pyridine (1.94 mL) were used as in general procedure XIII. The reaction mixture was concentrated in vacuo and the resulting solid was dissolved in ethanol. Water was added to the mixture and the resulting solid was filtered and washed with ether to afford **387** as a pink solid (0.309 g, 38%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.7 (s, 2H), 6.95 (d, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 7.5 (m, 2H), 7.55-7.65 (m, 3H), 7.79 (d, 2H), 7.9 (s, 1H), 8 (s, 1H), 9.89 (s, 1H), 12.85 (bs, 1H); MS (ES$^+$) *m/z* 406 (M+H)$^+$.

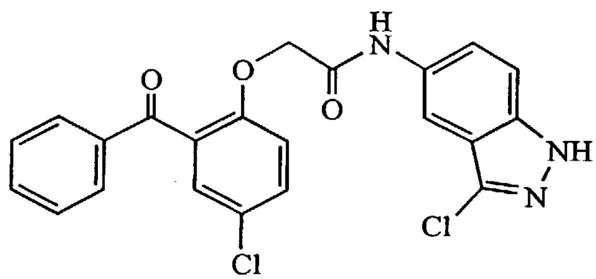
<u>Example</u> 166



388

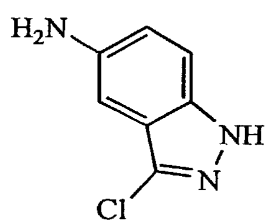
N,N-dimethyl-3-chloropropyl amine in acetone (5 mL) and water (4 drops) was added dropwise to a suspension of compound **385** (1.04 g, 2.5 mmol), acetone (10 mL), and potassium carbonate (2.82 g, 20.4 mmol) and then refluxed for 3 d under nitrogen. The suspension was cooled to rt and water and brine were added. The mixture was extracted with methylene chloride. To the organic layer was added 1N HCl in Et_2O (3 mL) and the resulting solution was concentrated in vacuo. The concentrate was purified by flash chromatography using a gradient between 9:1 and 4:1 methylene chloride:methanol as elutant to give an oil. The oil was dissolved in methylene chloride and 1N HCl in Et_2O (3 mL) was added and the mixture was stored at rt for 7 d. The precipitate was filtered and washed with ether to afford **388** as a yellow orange solid (0.125 g, 10%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.8 (m, 2H), 2.28 (s, 6H), 2.5 (m, 2), 4 (t, 2H), 4.8 (s, 2H), 6.9 (d, 1H), 7.08 (d, 1H), 7.25 (d, 1H), 7.45-7.58 (m, 4H), 7.65 (m, 2H), 7.8 (d, 2H), 9.05 (s, 1H); MS (ES$^+$) *m/z* 502 (M+H)$^+$.

<u>Example</u> 167



389

Step A:



390

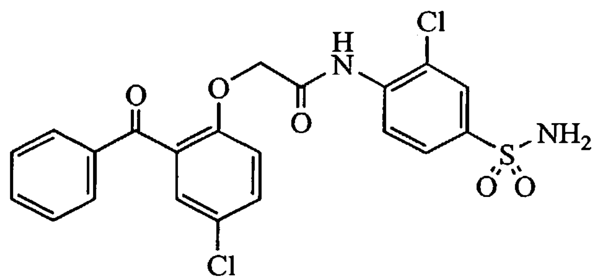
3-Chloro-5-nitroindazole (Lancaster, 5 g, 25 mmol), sodium dithionite (17.6 g, 101 mmol), ethanol (150 mL), and water (50 mL) were combined in a round-bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand and then refluxed overnight. The reaction mixture was concentrated in vacuo and the resulting solid was dissolved in ethyl acetate, washed with brine and water. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to give **390** as a yellow solid (1.3 g, 31%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5 (s, 2H), 6.55 (s, 1H), 6.8 (d, 1H), 7.2 (s, 1H), 12.7 (s, 1H); MS (ES$^+$) *m/z* 168 (M+H)$^+$. The crude product was used without further purification.

Step B:

Carboxylic acid **105** (2.25 g, 7.74 mmol), HCA (0.59 mL, 3.88 mmol), THF, PPh_3 (2.03 g, 7.74 mmol) in THF, compound **390** (1.3 g, 7.7 mmol) in THF (45 mL total reaction volume), and pyridine (7.5 mL, 93 mmol) were used as in general procedure XIII. The reaction mixture was concentrated in vacuo and the resulting solid was suspended in ethanol, methanol, acetone, and water. The resulting solid was filtered off and recrystallized from ethyl acetate:hexanes. The precipitate was filtered and washed with

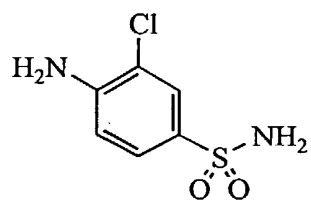
ether and 7:3 ethyl acetate:hexanes to afford **389** as a tan solid (0.87 g, 26%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.7 (s, 2H), 7.2 (d, 1H), 7.35 (d, 1H), 7.415 (s, 1H), 7.43-7.52 (m, 4H), 7.55-7.6 (m, 4H), 7.78 (m, 2H), 7.9 (s, 1H), 9.88 (s, 1H), 13.2 (s, 1H).

Example 168



391

Step A:



392

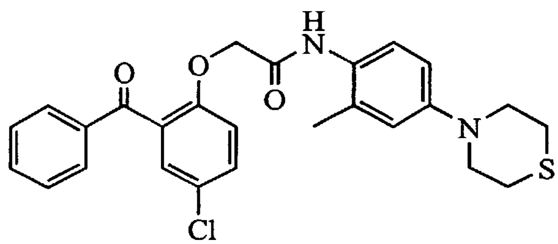
Ammonium hydroxide (40 mL) was added to 3-chloro-4-aminosulfonyl fluoride (Maybridge, 0.5 g, 2.4 mmol) and the mixture was heated to 62 °C for 1 h under nitrogen. The reaction was cooled to rt and the resulting mixture was extracted with ethyl acetate. The organics were dried over $MgSO_4$ and concentrated in vacuo to give **392** as a white solid (0.394 g, 80%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.07 (s, 2H), 6.8 (d, 1H), 7 (s, 2H), 7.39 (dd, 1H), 7.55 (d, 1H); MS (ES$^-$) *m/z* 205 (M-H)$^-$.

Step B:

Carboxylic acid **105** (0.54 g, 1.9 mmol), HCA (0.14 mL, 0.92 mmol), THF, PPh_3 (0.49 g, 1.9 mmol) in THF, compound **392** (0.384 g, 1.9 mmol), in THF (40 mL total reaction volume), and pyridine (1.8 mL) were used as in general procedure XIII. The reaction mixture was concentrated and the resulting solid was dissolved in ethanol. Water was

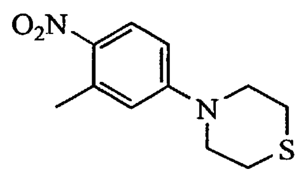
added and the precipitate was filtered and washed with 1:1 ethanol:water and ether to afford **391** as a white solid (0.206 g, 23.1%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.8 (s, 2H), 7.2 (d, 1H), 7.43 (s, 2H), 7.47 (m, 2H), 7.6 (m, 2H), 7.75 (dd, 3H), 7.8 (d, 1H), 8.05 (d, 1H), 9.3 (s, 1H).

Example 169



393

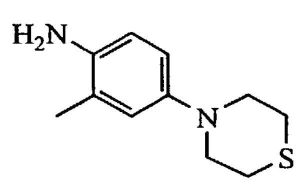
Step A:



394

5-Fluoro-2-nitrotoluene (Aldrich, 50.6 g, 364 mmol), DMSO (60 mL), and thiomorpholine (37 mL, 368 mmol) were combined and heated to 75°C for 2 h and 100°C for 4h under nitrogen. The reaction was cooled to rt. Ether was added to the mixture and the slurry was stirred vigorously. Water was added to the slurry and the resulting solid was filtered and washed with water and ether, then dissolved in methylene chloride. The organics were washed with water, dried over $MgSO_4$, and concentrated in vacuo to give **394** as a yellow solid (70 g, 81%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.5 (s, 3H), 2.6 (t, 4H), 3.8 (d, 1H), 6.85 (s, 1H), 7.95 (d, 1H). The crude product was used without further purification.

Step B:



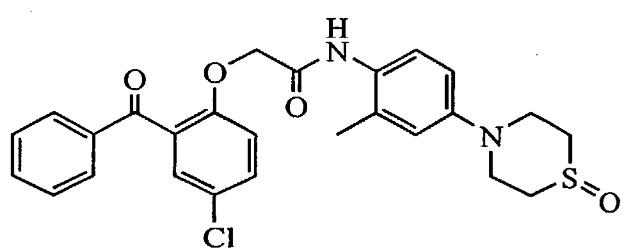
395

Compound **394** (0.29 g, 1.22 mmol), palladium on carbon (0.1 g, 10% w/w), ethanol (7 mL), and THF (7 mL) were used as in general procedure XII using 68 psi of hydrogen to afford **395** as a brown solid (0.252 g, crude material).

Step C:

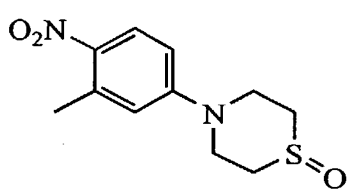
Compound **395** (0.252 g, 1.2 mmol), acetonitrile (12 mL), Et_3N (0.3 mL, 2.1 mmol), and acid chloride **320** (0.38 g, 1.2 mmol) were used as in general procedure X. The product was purified by flash chromatography using 7:3 hexanes:ethyl acetate as elutant to afford **393** as an orange solid (0.084 g, 14%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.95 (d, 3H), 2.6 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.67 (s, 2H), 6.75 (dd, 1H), 6.8 (d, 1H), 7.1 (d, 1H), 7.2 (d, 1H), 7.42 (d, 1H), 7.48 (t, 2H), 7.59 (t, 2H), 7.75 (d, 2H), 8.8 (s, 1H).

<u>**Example 170**</u>

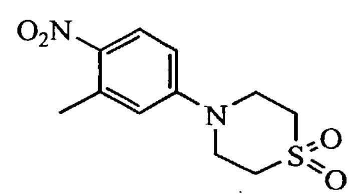


396

Step A:



397

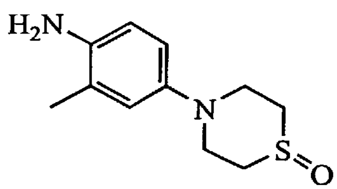


398

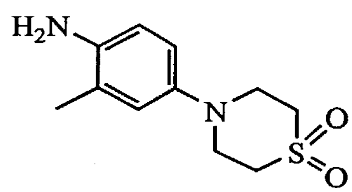
3-chloroperoxybenzoic acid (Aldrich, 0.046 g, 2.7 mmol) in methylene chloride was added dropwise to a stirred solution of compound **394** (12.5 g, 52.4 mmol) in methylene chloride (300 mL total volume for reaction) at -20 °C and the mixture was stirred for 1.5 h after

which the cooling bath was removed and the reaction was stirred at rt overnight under nitrogen. The mixture was washed with saturated sodium metabisulfite, 2N NaOH, and water. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to give a mixture of **397** and **398** as a yellow solid (12.2 g, crude mixture).

Step B:



399



400

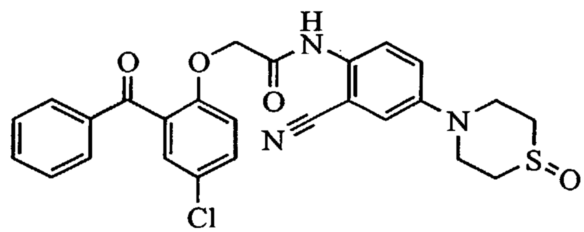
The mixture of **397** and **398** (12.3 g), palladium on carbon (3.7 g, 10% w/w), ethanol (100 mL), THF (30 mL), and methanol (75 mL) were used as in general procedure XII using 60 psi of hydrogen to afford an oil. The product was purified on silica gel by flash chromatography using 7:3 hexanes:ethyl acetate, 100% ethyl acetate, and 4:1 ethyl acetate:methanol as elutants to afford **399** as an orange solid (4.27 g, 39%) ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.99 (s, 3H), 2.68 (d, 2H), 2.87 (t, 2H), 3.15 (dd, 2H), 3.44 (t, 2H), 4.38 (bs, 2H), 6.49 (d, 1H), 6.59 (d, 1H), 6.64 (s, 1H); MS (ES$^+$) *m/z* 225 $(M+H)^+$ and **400** as a tan solid (3.57 g, 31%) ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.99 (s, 3H), 3.08 (m, 4H), 3.42 (m, 4H), 4.42 (bs, 2H), 6.49 (d, 1H), 6.59 (d, 1H), 6.66 (d, 1H); MS (ES$^+$) *m/z* 241 $(M+H)^+$.

Step C:

Carboxylic acid **105** (2.02 g, 6.95 mmol), HCA (0.528 mL, 3.48 mmol), THF (20 mL), PPh_3 (1.82 g, 6.95 mmol) in THF (15 mL), sulfoxide **399** (1.56 g, 6.95 mmol) in THF (125 mL total reaction volume), and pyridine (6.75 mL, 83.5 mmol) were used as in general procedure XIII. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The concentrate was purified by flash chromatography using a gradient between 99:1 and 4:1 methylene chloride:methanol as elutant to afford **396** as a yellow foam (1.62 g, 47%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.95 (d, 3H), 2.62 (dd, 2H), 2.86 (t, 2H), 3.5

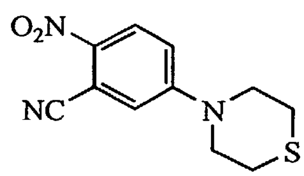
(dd, 2H), 3.69 (t, 2H), 4.67 (s, 2H), 6.75 (dd, 1H), 6.8 (d, 1H), 7.1 (d, 1H), 7.2 (d, 1H), 7.42 (d, 1H), 7.48 (t, 2H), 7.59 (t, 2H), 7.75 (d, 2H), 8.8 (s, 1H).

Example 171



401

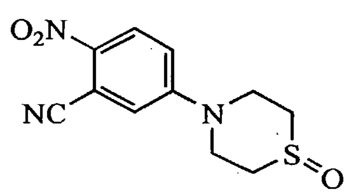
Step A:



402

5-Chloro-2-nitrobenzonitrile (Aldrich, 5 g, 27.4 mmol), sodium bicarbonate (4.62 g, 55 mmol), pyridine (40 mL), water (1 mL), and thiomorpholine (5.53 mL, 55 mmol) were used as in general procedure XI to afford **402** as an orange solid (5.19 g, 76%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.62 (m, 4H), 3.9 (m, 4H), 7.2 (d, 1H), 7.5 (d, 1H), 8.1 (d, 1H). The crude product was used without purification.

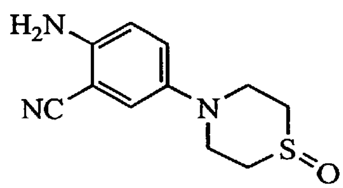
Step B:



403

3-Chloroperoxybenzoic acid (Aldrich, 4.85 g, 17 mmol) in methylene chloride was added to a cooled solution of compound **402** (3 g, 12 mmol) in methylene chloride (100 mL total volume for reaction) at -20°C and the mixture was stirred for 15 min. after which the cooling bath was removed and the mixture was stirred at rt for 4 h under nitrogen. The

reaction mixture was washed with saturated sodium metabisulfite, 2N NaOH, and brine. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to afford **403** as a yellow solid (0.59 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.63 (m, 4H), 3.9 (m, 4H), 7.2 (dd, 1H), 7.5 (d, 1H), 8.1 (d, 1H).



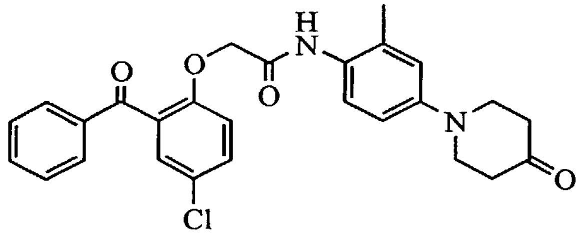
404

Palladium on carbon (0.23 g, 10% w/w), compound **403** (0.5 g, 1.9 mmol), ethanol (30 mL total reaction volume), THF (20 mL), and methanol (20 mL) were used as in general procedure XII to afford **404** as a green oil (0.41 g, 93%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.68 (d, 2H), 2.9 (t, 2H), 3.3 (d, 2H), 3.55 (t, 2H), 5.6 (bs, 2H), 6.79 (d, 1H), 7.02 (d, 1H), 7.17 (dd, 1H).

Step C:

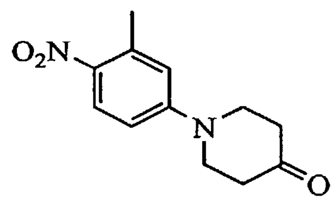
Compound **404** (0.41 g, 1.8 mmol), HCA (0.132 mL, 0.87 mmol), PPh_3 (0.46 g, 1.75 mmol), pyridine (1.7 mL, 21 mmol), THF (25 mL), and carboxylic acid **105** (0.51 g, 1.8 mmol) were used as in general procedure XIII. The concentrate was purified by flash chromatography using 95:5 methylene chloride:methanol as elutant, flash chromatography using a gradient between 7:3 hexanes:ethyl acetate and 4:1 ethyl acetate:methanol as elutant, TLC prep plate using 9:1 methylene chloride:methanol with 0.1% Et_3N as elutant. The concentrate was dissolved in methylene chloride and washed with 2N HCl. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to afford **401** as a tan foam (0.145 g, 16%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.65 (d, 2H), 2.9 (t, 2H), 3.8 (m, 4H), 4.76 (s, 2H), 7.2 – 7.4 (m, 3H), 7.4 – 7.6 (m, 4H), 7.65 (m, 2H), 7.8 (d, 2H), 9.7 (s, 1H).

Example 172



405

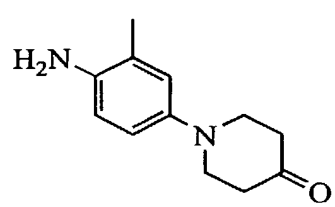
Step A:



406

4-Piperidone monohydrate monohydrochloride salt (Lancaster, 2.73 g, 17.8 mmol) and saturated potassium carbonate (10 mL) were combined in a round-bottom flask and stirred for 10 min. Pyridine (45 mL) and 2-nitro-5-fluorotoluene (Aldrich, 1.41 mL, 9.35 mmol) were added and the reaction was refluxed overnight. The two-phase solution was separated and the organics were concentrated in vacuo. The concentrate was dissolved in ethyl acetate and washed with water and brine. The organics were dried over $MgSO_4$ and concentrated in vacuo to afford **406** as a red oil (0.59 g, 27). ^1H NMR (DMSO-d_6, 300 MHz) δ 2.6 (t, 4H), 3.8 (t, 4H), 7 (d, 2H), 8 (d, 2H); MS (ES^+) *m/z* 235 $(M+H)^+$.

Step B:

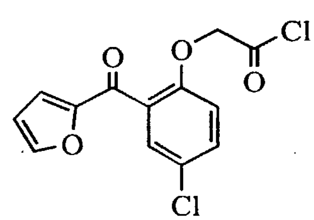


407

Compound **406** (0.57 g, 2.4 mmol), palladium on carbon (0.17 g, 10% w/w), ethanol (25 mL) and THF (25 mL) were used as in general procedure XII using 70 psi hydrogen to afford **407** as a yellow oil (0.5 g, crude material).

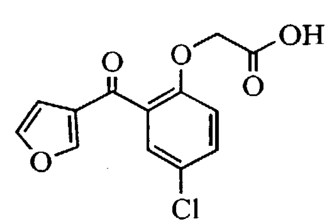
Step C:

Compound **407** (0.5 g, 2.1 mmol), HCA (0.16 mL, 1.05 mmol), PPh_3 (0.56 g, 2.1 mmol), pyridine (2 mL, 25 mmol), THF (50 mL), and carboxylic acid **105** (0.62 g, 2.1 mmol) were used as in general procedure XIII. The mixture was concentrated in vacuo and purified on by flash chromatography using a gradient between 1:1 hexanes:ethyl acetate and 100% ethyl acetate as elutant to afford **405** as a yellow solid (0.32 g, 31%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2 (s, 3H), 2.4 (m, 4H), 3.58 (m, 4H), 4.7 (s, 2H), 6.85 (d, 1H), 6.9 (s, 1H), 7.15 (d, 1H), 7.25 (d, 1H), 7.48 (s, 1H), 7.55 (t, 2H), 7.65 (t, 2H), 7.8 (d, 2H), 8.85 (s, 1H); MS (ES$^+$) *m/z* 478 (M+H)$^+$.



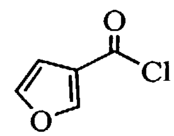
408

Carboxylic acid **115** (1 g, 3.6 mmol), methylene chloride (30 mL), and thionyl chloride (7.6 mL, 104 mmol) were used as in general procedure XV to afford **408** as a purple oil (1.24 g, crude material).



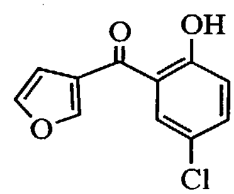
409

Ester **412** (15.92 g, 52 mmol), ethanol (EtOH, 150 mL), water (50 mL), and lithium hydroxide monohydrate (2.71 g, 65 mmol) were used as in general procedure IV to afford **409** as a tan solid (7.47 g, 51.6%). The crude material was used without purification.



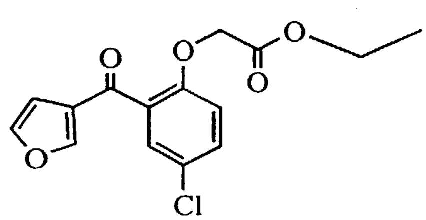
410

Thionyl chloride (60 mL, 800 mmol) was added portionwise to a solution of 3-furoic acid (11.21 g, 100 mmol) in methylene chloride (100 mL) and the mixture was refluxed for 2 h. The solution was concentrated in vacuo to afford the acid chloride **410** as an oil (13 g, crude material).



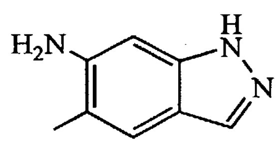
411

Acid chloride **410** (13 g, 100 mmol), aluminum chloride ($AlCl_3$, 13.6 g, 100 mmol), CH_2Cl_2 (200 mL), and 4-chloroanisole (12.25 mL, 100 mmol) were used as in general procedure III. The product was purified by flash chromatography using a 7:3 hexanes:methylene chloride and 1:1 hexanes:methylene chloride as elutant. The concentrate was triturated between ether and hexanes, filtered, and the resulting solid was washed with hexanes to afford **411** as a yellow crystalline solid (12.3 g, 55%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.8 (s, 1H), 6.95 (d, 1H), 7.4 (m, 2H), 7.8 (s, 1H), 8.25 (s, 1H), 10.45 (s, 1H).



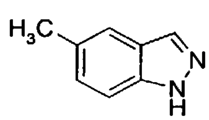
412

Phenol **411** (12.3 g, 55.3 mmol), potassium carbonate (38.21 g, 277 mmol), ethyl bromoacetate (6.4 mL, 57.7 mmol), and acetone (250 mL) were used as in general procedure II to afford **412** as a yellow/orange foam (15.9 g, 93%). MS (ES$^-$) *m/z* 279 (M-H)$^-$. The crude product was used without purification.



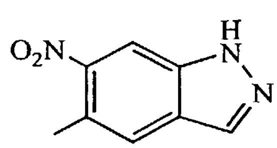
413

Compound **415** (0.4 g, 2.3 mmol), palladium on carbon (0.12 g, 10% w/w), and ethanol (50 mL) were used as in general procedure XII using 60 psi of hydrogen to afford **413** as a tan solid (0.35 g, crude material). ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 2.05 (s, 3H), 4.96 (bs, 2H), 6.56 (s, 1H), 7.22 (s, 1H), 7.63 (s, 1H), 12.16 (s, 1H); MS (ES$^-$) *m/z* 148 (M-H)$^-$.



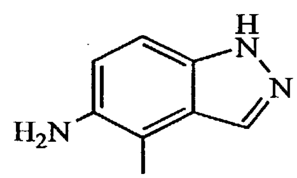
414

Potassium nitrate (10.13 mL, 100 mmol) in concentrated sulfuric acid (50 mL) was added dropwise to a stirred solution of concentrated sulfuric acid (50 mL) and 2,4-dimethylaniline (Aldrich, 4.94 g, 40.8 mmol) at 0 °C. The reaction was stirred for 3 h. The mixture was poured into ice water (1800 mL) and extracted with ethyl acetate. The organics were separated and concentrated in vacuo to afford **414** as an orange solid (2.98 g, 44%). ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 2.02 (s, 3H), 2.3 (s, 3H), 7 (s, 1H), 7.26 (s, 1H).



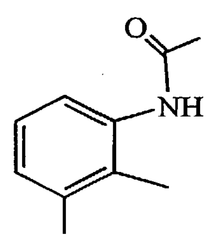
415

Sodium nitrite (0.67 g, 9.7 mmol) in water (4 mL) was added dropwise to a stirred solution of compound **414** (1.6 g, 9.6 mmol) and glacial acetic acid (250 mL) at 0 °C. The reaction was stirred for 15 min. at 0 °C, and rt for 3 h. The reaction was stored for 9 d. The mixture was concentrated in vacuo. The concentrate was triturated with water and the resulting slurry was stirred for 1 h. The slurry was filtered and washed with water. The solid was dissolved in methylene chloride and washed with water. The organics were separated and further purified by flash chromatography using 9:1 hexanes:ethyl acetate and 1:1 hexanes:ethyl acetate to afford **415** as a red solid (0.4 g, 19%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.5 (s, 3H), 7.82 (s, 1H), 8.17 (d, 2H), 13.53 (bs, 1H).



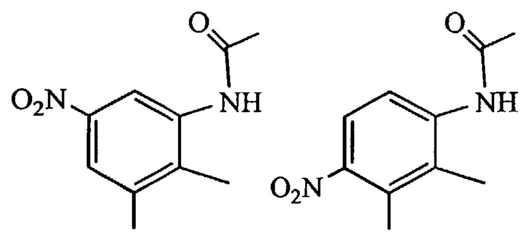
416

Compound **420** (1.07 g, 6 mmol), palladium on carbon (0.33 g, 10% w/w), ethanol (30 mL) and THF (20 mL) were used as in general procedure XII using 80 psi of hydrogen to afford **416** as a brown solid (0.53 g, 60%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.25 (s, 3H), 4.5 (s, 2H), 6.8 (d, 1H), 7.1 (d, 1H), 7.85 (s, 1H), 12.55 (bs, 1H). MS (ES$^-$) *m/z* 148 (M-H)$^-$.



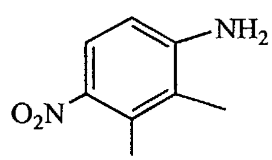
417

Acetic anhydride (25 mL, 265 mmol) was added to a stirred solution of 2,3-dimethylaniline (Aldrich, 31.2 g, 257 mmol) and toluene (50 mL) under nitrogen. The resulting solid was filtered and washed with hexanes and ether to afford **417** as a white solid (40.59 g, crude material). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.06 (d, 6H), 2.26 (s, 3H), 7.05 (m, 2H), 7.15 (d, 1H), 9.35 (bs, 1H).



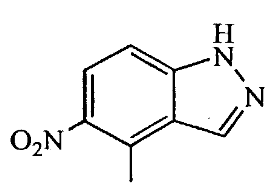
418

Potassium nitrate (6.2 g, 61 mmol) in concentrated sulfuric acid (75 mL) was added dropwise over 1 h to a cooled, stirred solution of concentrated sulfuric acid (50 mL) and compound **417** (10 g, 61 mmol) at -17 °C. The cooling bath was removed and the reaction was stirred at 0 °C for 1 h. The solution was poured into ice water (2000 mL) and stirred vigorously. The solution was extracted with methylene chloride. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to afford a solid. The solid was purified by flash chromatography using a gradient between 7:3 hexanes:ethyl acetate and ethyl acetate as elutant to afford **418** as a yellow solid (4.24g, 33%). MS (ES^-) *m/z* 201 $(M-H)^-$. Compound **418** was used as a mixture without purification.



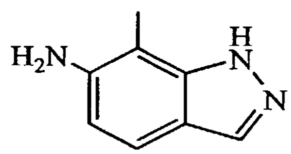
419

Compound **418** (4.24 g, 20.4 mmol) was added portionwise to a stirred solution of potassium hydroxide (1.2 g, 21 mmol), water (50 mL), and ethanol (200 mL) and the mixture was refluxed for 1 h. Water (50 mL) was added to the reaction dropwise and the resulting solution was cooled to rt. A precipitate was filtered and washed with water and ether. The filtrate was extracted with ether and the organics were combined, dried over $MgSO_4$, and concentrated in vacuo to give **419** as a yellow solid (2.02 g, 60%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2 (s, 3H), 2.34 (s, 3H), 6.12 (bs, 2H), 6.5 (d, 1H), 7.6 (d, 1H).



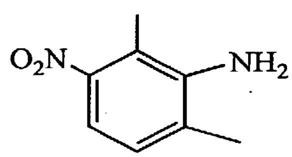
420

Sodium nitrite (0.42 g, 6 mmol) in water was added dropwise to a stirred solution of compound **419** (1 g, 6 mmol) and glacial acetic acid (50 mL) at 0°C and stirred for 1 h. The reaction was stored for 2 d at rt. The mixture was concentrated in vacuo and the concentrate was triturated with water. The resulting solid was filtered and washed with water to afford **420** as a tan solid (2.07 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.8 (s, 3H), 7.5 (d, 1H), 7.95 (d, 1H), 8.45 (s, 1H), 13.6 (bs, 1H); MS (ES$^-$) *m/z* 176 (M-H)$^-$.



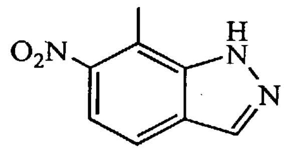
421

Compound **423** (2.69 g, 15.2 mmol), palladium on carbon (0.8 g, 10% w/w), ethanol (100 mL), and THF (20 mL) were used as in general procedure XII using 60 psi of hydrogen to afford **421** as a tan solid (1.43 g, 63.8%). The crude material was used without purification.



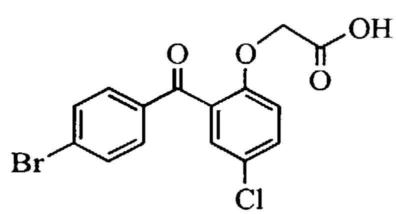
422

Potassium nitrate (10.13 mL, 100 mmol) in concentrated sulfuric acid (50 mL) was added dropwise to a stirred solution of concentrated sulfuric acid (50 mL) and 2,6-dimethylaniline (Aldrich, 12.32 g, 100 mmol) at -10 °C and stirred for 1 h. The mixture was poured into ice water and extracted with ethyl acetate. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo to afford **422** as an orange solid (5.63 g, 34%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.05 (d, 6H), 5.4 (bs, 2H), 6.9 (d, 1H), 6.96 (d, 2H). The crude material was used without purification.



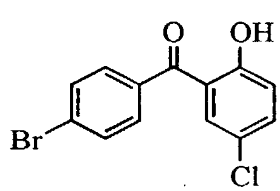
423

Sodium nitrite (2.34 g, 34 mmol) in water (10 mL) was added dropwise to a stirred solution of compound **422** (5.63 g, 34 mmol) and glacial acetic acid (500 mL) at 0°C and stirred for 15 min. The cooling bath was removed and the reaction was stored at rt for 6 d. The mixture was concentrated in vacuo and the concentrate was triturated with water. The resulting solid was filtered and recrystallized from methanol to give **423** as a red solid (2.69 g, 45%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.73 (s, 3H), 3.15 (s, 3H), 7.64 (d, 1H), 7.9 (d, 1H), 8.24 (s, 1H), 13.85 (bs, 1H). MS (ES$^-$) *m/z* 176 (M-H)$^-$. The crude material was used without purification.



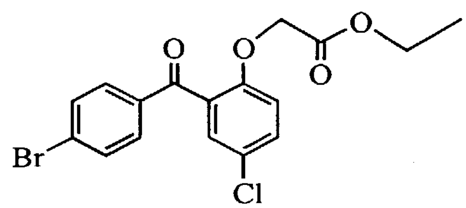
424

Ester **426** (16.72 g, 42 mmol), ethanol (EtOH, 200 mL), water (50 mL), and lithium hydroxide monohydrate (2.21 g, 52 mmol) were used as in general procedure III to afford **424** as an off-white solid (10.71 g, 69%). The crude material was used without purification.



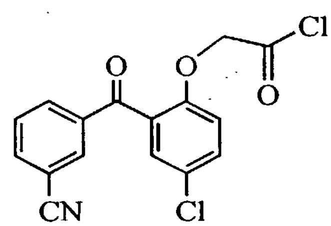
425

4-Bromobenzoyl chloride (8.73 g, 40 mmol), aluminum chloride ($AlCl_3$, 5.3 g, 40 mmol), CH_2Cl_2 (125 mL), and 4-chloroanisole (4.87 mL, 40 mmol) were used as in general procedure I to afford **425** as a yellow solid (14.27 g, crude material).



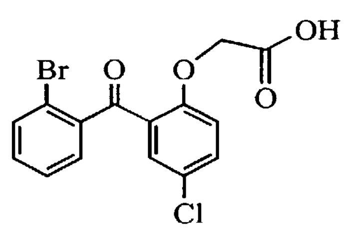
426

Compound **425** (14.27 g, 65 mmol), potassium carbonate (45 g, 325 mmol), ethyl bromoacetate (7.57 mL, 68 mmol), and acetone (250 mL) were used as in general procedure II to afford **426** as a tan solid (16.72 g, 65%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.6(s, 2H), 7.07 (d, 1H), 7.4 (d, 1H), 7.54 (dd, 1H), 7.64 (m, 4H), 13.04 (bs, 1H). The crude material was used without purification.



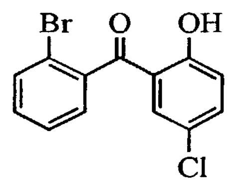
427

Carboxylic acid **129** (1.5 g, 4.8 mmol), methylene chloride (30 mL), and thionyl chloride(10 mL, 137 mmol) were used as in general procedure XV to afford **427** as an off-white, sticky solid (1.58 g, crude material).



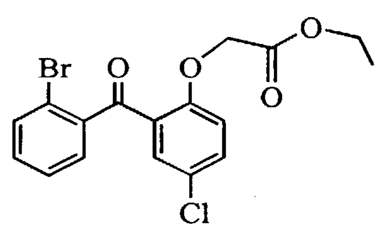
428

Ester **430** (17.24 g, 43 mmol), ethanol (200 mL), water (50 mL), and lithium hydroxide monohydrate (2.27 g, 54 mmol) were used as in general procedure III to afford **123** as a white solid (6.53 g, 41%).



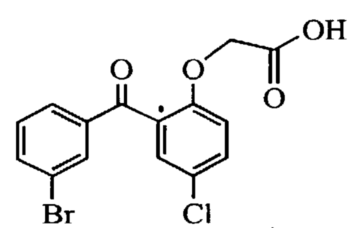
429

2-Bromobenzoyl chloride (10 g, 46 mmol), aluminum chloride ($AlCl_3$, 6.2 g, 46 mmol), CH_2Cl_2 (250 mL), and 4-chloroanisole (5.6 mL, 46 mmol) were used as in general procedure I to afford **429** as a tan solid (13.76 g, crude material).



430

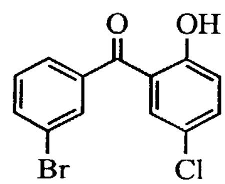
Compound **429** (13.76 g, 44 mmol), potassium carbonate (30.52 g, 221 mmol), ethyl bromoacetate (5.14 mL, 46 mmol), and acetone (250 mL) were used as in general procedure II to afford **430** as a yellow solid (17.24 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.5 (s, 2H), 7.15 (d, 1H), 7.4 (s, 4H), 7.48 (d, 1H), 7.58 (d, 1H), 7.65 (d, 1H), 12.95 (bs, 1H).



431

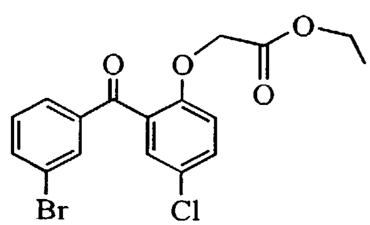
Ester **433** (17.24 g, 43 mmol), ethanol (EtOH, 200 mL), water (50 mL), and lithium hydroxide monohydrate (2.27 g, 54 mmol) were used as in general procedure III to afford

431 as a white solid (6.53 g, 41%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.65 (s, 2H), 7.08 (d, 1H), 7.42 (m, 2H), 7.54 (dd, 1H), 7.71 (d, 1H), 7.83 (dd, 2H), 13.00 (bs, 1H); MS (ES$^+$) *m/z* 371 (M+H)$^+$. The crude material was used without purification.



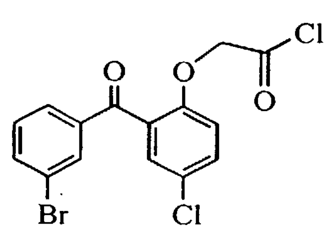
432

3-Bromobenzoyl chloride (24.11 g, 110 mmol), aluminum chloride ($AlCl_3$, 15 g, 113 mmol), CH_2Cl_2 (250 mL), and 4-chloroanisole (13.46 mL, 110 mmol) were used as in general procedure I to afford, after triturating the concentrate with hexanes and filtering, **432** as a green solid (25.57 g, 75%). The crude material was used without purification.



433

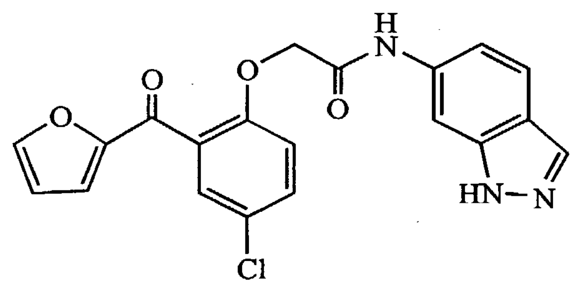
Compound **432** (9.08 g, 29 mmol), potassium carbonate (20.14 g, 146 mmol), ethyl bromoacetate (3.39 mL, 31 mmol), and acetone (200 mL) were used as in general procedure II to afford **433** as a red/brown oil (12.68 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.12 (t, 3H), 4.06 (q, 2H), 4.75 (s, 2H), 7.11 (d, 1H), 7.44 (t, 2H), 7.54 (d, 1H), 7.69 (d, 1H), 7.83 (d, 2H); MS (ES$^+$) *m/z* 398 (M+H)$^+$.



434

Carboxylic acid **431** (3 g, 8.1 mmol), methylene chloride (25 mL), and thionyl chloride(11.84 mL, 162 mmol) were used as in general procedure XV to afford **434** as a light brown oil (2.96 g, 94%). The crude material was used without purification.

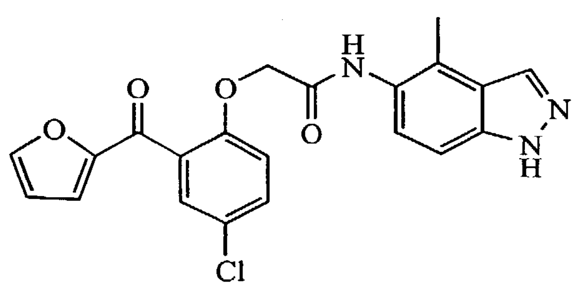
Example 173



435

Compound **115** (0.28 g, 1 mmol), HCA (0.08 mL, 0.5 mmol), THF (50 mL total reaction volume), PPh_3 (0.26 g, 1 mmol) in THF, and 6-aminoindazole (0.13 g, 1 mmol) in THF were used as in general procedure XIII. The product was purified by flash chromatography using a gradient between 1:1 hexanes:ethyl acetate and 100% ethyl acetate to afford **435** as an orange oil (0.042 g, 11%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.8 (s, 2H), 6.7 (d, 1H), 7.05 (d, 1H), 7.2 (d, 2H), 7.35 (d, 1H), 7.5 (d, 1H), 7.55 (dd, 1H), 7.65 (d, 1H), 7.94 (s, 1H), 8.07 (s, 2H), 10.06 (s, 1H), 12.89 (s, 1H).

Example 174

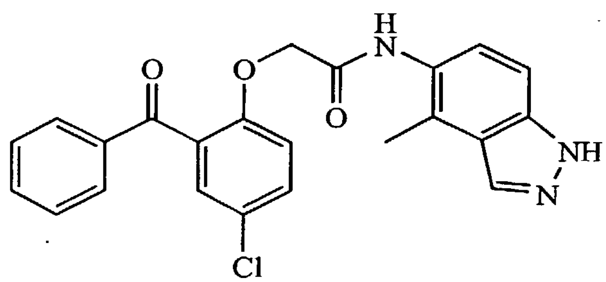


436

Compound **115** (0.19g, 0.68 mmol), HOBt (0.09 g, 0.68 mmol), DMF (1 mL), **416** (0.1 g, 0.68 mmol) in DMF, EDAC (0.13 g, 0.69 mmol) in DMF (5 mL total reaction volume), and Et_3N (0.19 mL, 1.36 mmol) were used as in general procedure IV. The product was

purified by flash chromatography using 1:1 and 7:3 ethyl acetate:hexanes to afford **436** as an off-white solid (0.126 g, 11%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.25 (s, 3H), 4.8 (s, 2H), 6.7 (s, 1H), 7.18-7.35 (m, 4H), 7.5 (s, 1H), 7.6 (d, 1H), 8.05 (dd, 2H), 9.35 (s, 1H), 13 (s, 1H).

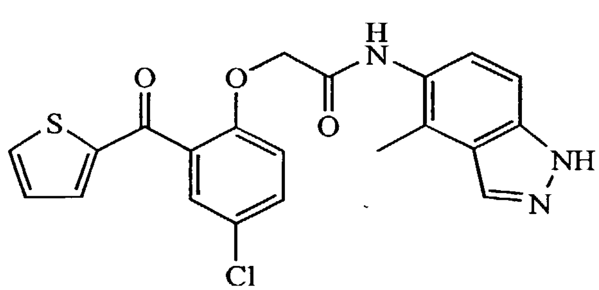
Example 175



437

Compound **416** (0.1 g, 0.68 mmol), NEt_3 (0.14 mL, 0.71 mmol), acetonitrile (5 mL total reaction volume), and acid chloride **1** (0.53 g, 1.7 mmol) in acetonitrile were used as in general procedure X. The product was purified by flash chromatography using 1:1 hexanes:ethyl acetate to afford **437** as an off-white solid (0.095 g, 33%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.28 (s, 3H), 4.78 (s, 2H), 7.15 (d, 1H), 7.3 (t, 2H), 7.55 (dd, 3H), 7.65 (t, 2H), 7.82 (d, 2H), 8.13 (s, 1H), 9.18 (s, 1H), 13.04 (bs, 1H); MS (ES$^+$) *m/z* 420 $(M+H)^+$.

Example 176

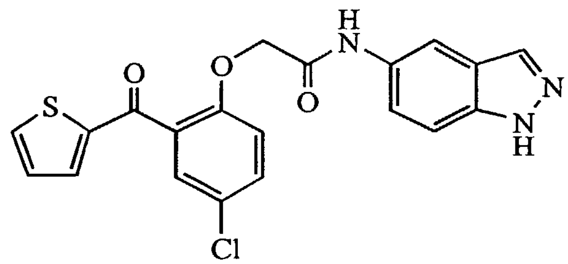


438

Compound **112** (0.20g, 0.67 mmol), HOBt (0.09 g, 0.68 mmol), DMF (2 mL), compound **416** (0.1 g, 0.68 mmol) in DMF (3 mL), EDAC (0.13 g, 0.69 mmol), and Et_3N (0.19 mL, 1.36 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 7:3 ethyl acetate:hexanes and 100% ethyl acetate to afford **438** as

an off-white solid (0.192 g, 67%). [1]H NMR (DMSO-d_6, 300 MHz) δ 2.3 (s, 3H), 4.85 (s, 2H), 7.2-7.35 (m, 4H), 7.55 (s, 1H), 7.65 (d, 1H), 7.7 (s, 1H), 8.15 (s, 2H), 9.38 (s, 1H), 13.05 (s, 1H); MS (ES^-) *m/z* 424 $(M-H)^-$.

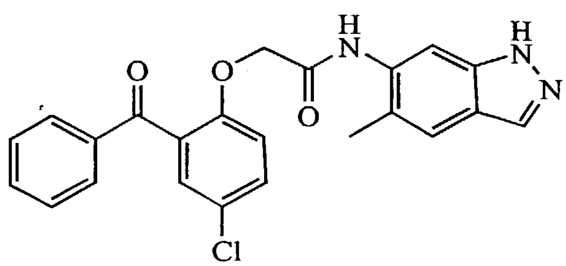
Example 177



439

Compound **112** (0.20g, 0.67 mmol), HOBt (0.09 g, 0.68 mmol), DMF (2 mL), 5-aminoindazole (Aldrich, 0.09 g, 0.68 mmol) in DMF (3 mL), EDAC (0.13 g, 0.69 mmol), and Et_3N (0.19 mL, 1.36 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 1:1 ethyl acetate:hexanes as elutant and further purified by dissolving in ethyl acetate, washing with water, drying organics over $MgSO_4$ and concentrating in vacuo to afford **439** as an off-white solid (0.071 g, 26%). [1]H NMR (DMSO-d_6, 400 MHz) δ 4.8 (s, 2H), 7.2 (d, 2H), 7.35 (d, 1H), 7.5 (d, 2H), 7.55 (d, 1H), 7.65 (s, 1H), 8 (t, 3H), 9.85 (s, 1H), 13 (s, 1H).

Example 178

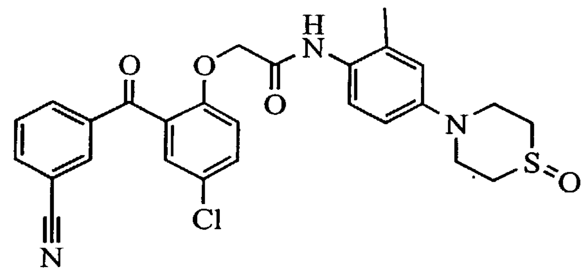


440

Compound **413** (0.1 g, 0.68 mmol), NEt_3 (0.19 mL, 2.6 mmol), acetonitrile (30 mL), and acid chloride **320** (0.21 g, 0.68 mmol) in acetonitrile (10 mL) were used as in general procedure X. The product was purified by flash chromatography using 7:3 hexanes:ethyl acetate then 1:1 hexanes:ethyl acetate as elutant, and a TLC prep plate eluted with 1:1 hexanes:ethyl acetate to afford **440** as an off-white solid (0.019 g, 6.7%). [1]H NMR

(DMSO-d_6, 300 MHz) δ 2.28 (s, 3H), 4.78 (s, 2H), 7.15 (d, 1H), 7.3 (t, 2H), 7.49 (m, 3H), 7.64 (t, 2H), 7.8 (d, 2H), 8.1 (s, 1H), 9.18 (s, 1H), 13 (bs, 1H); MS (ES$^+$) m/z 420 $(M+H)^+$.

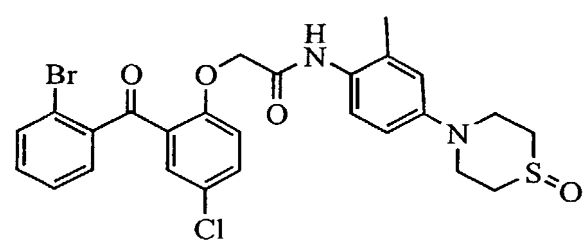
Example 179



441

Compound **399** (1.2 g, 5.4 mmol) in acetonitrile (45 mL total reaction volume),acid chloride **427** (1.22 g, 3.65 mmol) in acetonitrile, and NEt_3 (0.71 mL, 5.1 mmol) were used as in general procedure X. The product was purified by flash chromatography using 95:5 methylene chloride:methanol as elutant to afford **441** as an off-white solid (0.59 g, 31%). ^1H NMR (DMSO-d_6, 400 MHz) δ 1.97 (s, 3H), 2.6 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.67 (s, 2H), 6.75 (d, 1H), 6.82 (s, 1H), 7.06 (d, 1H), 7.2 (d, 1H), 7.48 (s, 1H), 7.65 (t, 2H), 8.05 (bs, 2H), 8.15 (s, 1H), 8.96 (s, 1H).

Example 180

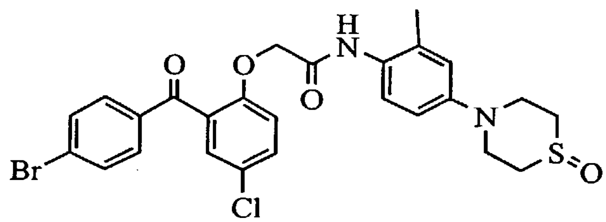


442

Compound **428** (0.443 g, 1.2 mmol), HOBt (0.16 g, 1.2 mmol), DMF, compound **399** (0.40 g, 1.8 mmol) in DMF (15 mL total reaction volume), EDAC (0.23 g, 1.2 mmol), and Et_3N (0.34 mL, 2.4 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **442** as an off-white foam (0.154 g, 22%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.07 (s, 3H), 2.6 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.62 (s, 2H), 6.78 (d, 1H), 6.84

(s, 1H), 7.15 (d, 1H), 7.25 (d, 1H), 7.38 (t, 1H), 7.42 (d, 2H), 7.5 (t, 1H), 7.65 (m, 2H), 8.8 (s, 1H).

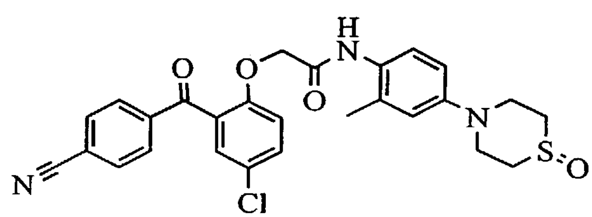
Example 181



443

Compound **424** (0.443 g, 1.2 mmol), HOBt (0.16 g, 1.2 mmol), DMF, compound **399** (0.40 g, 1.8 mmol) in DMF (15 mL total reaction volume), EDAC (0.23 g, 1.2 mmol), and Et_3N (0.34 mL, 2.4 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **443** as a pale yellow foam (0.105 g, 15%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.06 (s, 3H), 2.75 (d, 2H), 2.95 (t, 2H), 3.6 (d, 2H), 3.8 (t, 2H), 4.77 (s, 2H), 6.88 (d, 1H), 6.92 (s, 1H), 7.15 (d, 1H), 7.3 (d, 1H), 7.55 (d, 1H), 7.72 (d, 2H), 7.78 (s, 4H), 8.97 (s, 1H); MS (ES^-) *m/z* 574 $(M-H)^-$.

Example 182

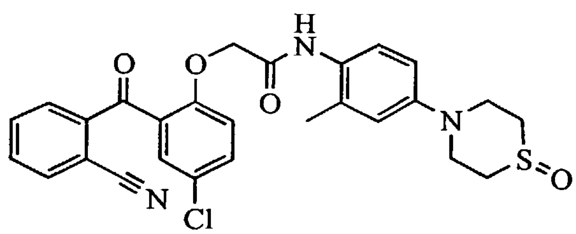


444

Copper cyanide (0.029 g, 0.33 mmol) was added to a solution of compound **443** (0.093 g, 0.16 mmol) in DMSO (5 mL) and the reaction was heated to 160°C and stirred overnight. The mixture was cooled and water was added to it. The resulting solid was filtered and washed with ethyl acetate. The filtrate was separated, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography using a gradient between 9:1 hexanes:ethyl acetate and ethyl acetate as the elutant to afford **444** as

an orange foam (0.012 g, 14%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.95 (s, 3H), 2.65 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.64 (s, 2H), 6.75 (dd, 1H), 6.82 (s, 1H), 7.02 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 7.63 (d, 2H), 7.9 (m, 4H), 8.88 (s, 1H); MS (ES$^-$) *m/z* 521 (M-H)$^-$.

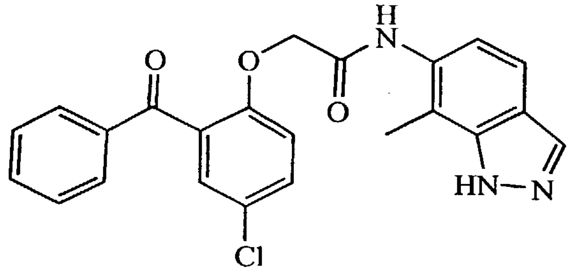
Example 183



445

Copper cyanide (0.037 g, 0.42 mmol) was added to a solution of compound **442** (0.120 g, 0.21 mmol) in DMSO (5 mL) and the reaction was heated to 160 °C and stirred overnight. The mixture was cooled and water was added to it. The resulting solid was filtered and washed with ethyl acetate. The filtrate was separated, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography using a gradient between 9:1 hexanes:ethyl acetate and ethyl acetate as the elutant to afford **445** as an orange foam (0.012 g, 11%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.99 (s, 3H), 2.62 (d, 2H), 2.86 (t, 2H), 3.5 (d, 2H), 3.69 (t, 2H), 4.62 (s, 2H), 6.75 (d, 1H), 6.82 (s, 1H), 7.05 (d, 1H), 7.2 (d, 1H), 7.55 (d, 1H), 7.7 (m, 4H), 7.98 (d, 1H), 8.97 (s, 1H); MS (ES$^-$) *m/z* 521 (M-H)$^-$.

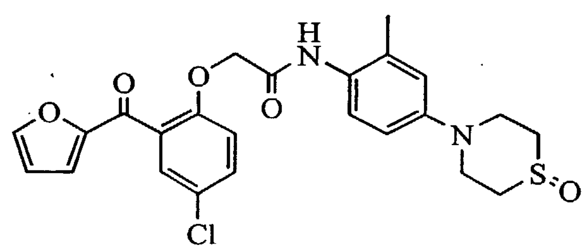
Example 184



446

Carboxylic acid **105** (0.296 g, 1.2 mmol), HOBt (0.136 g, 1.02 mmol), DMF, compound **421** (0.296 g, 1.02 mmol) in DMF (10 mL total reaction volume), EDAC (0.193 g, 1.02 mmol), and Et_3N (0.284 mL, 2.04 mmol) were used as in general procedure IV. The product was purified by flash chromatography using 1:1 ethyl acetate:hexanes as elutant. The concentrate was dissolved in methylene chloride, washed with 10% potassium carbonate. The organics were separated, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was triturated with ethyl acetate and filtered to afford **446** as an off-white solid (0.0081 g, 2%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.2 (s, 3H), 4.74 (s, 2H), 6.95 (d, 1H), 7.22 (d, 1H), 7.45 (m, 4H), 7.6 (m, 2H), 7.75 (d, 2H), 7.98 (s, 1H), 9.25 (s, 1H) 13.05 (bs, 1H); MS (ES^+) m/z 420 $(M+H)^+$.

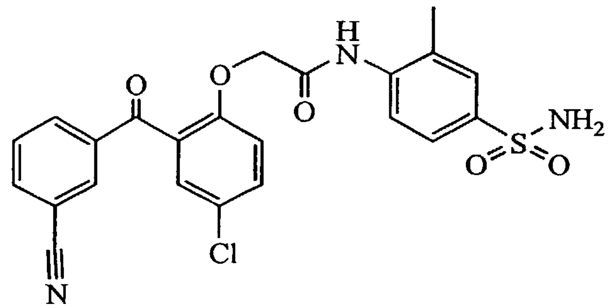
Example 185



447

Compound **399** (0.314 g, 1.4 mmol) in acetonitrile (10 mL total reaction volume), acid chloride **408** (0.3 g, 1 mmol) in acetonitrile, and NEt_3 (0.24 mL, 1.7 mmol) were used as in general procedure X. The product was dissolved in methylene chloride and washed with saturated potassium carbonate and water then purified by flash chromatography using 95:5 methylene chloride:methanol as elutant to afford **447** as an off-white foam (0.305 g, 63%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.03 (s, 3H), 2.63 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.74 (s, 2H), 6.71 (d, 1H), 6.78 (d, 1H), 6.84 (s, 1H), 7.18 (m, 2H), 7.3 (d, 1H), 7.5 (d, 1H), 7.59 (dd, 1H), 8.06 (s, 1H), 9.02 (s, 1H); MS (ES^+) m/z 487 $(M+H)^+$.

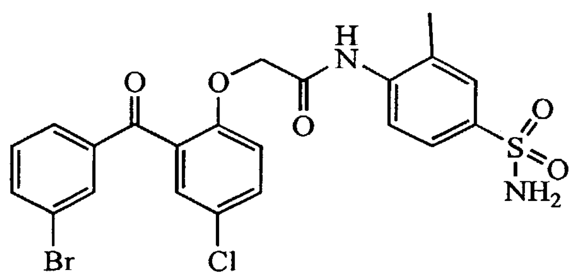
Example 187



448

Compound **466** (0.15 g, 0.8 mmol) in acetonitrile (10 mL total reaction volume), acid chloride **427** (0.2 g, 0.6 mmol) in acetonitrile, and NEt_3 (0.112 mL, 0.8 mmol) were used as in general procedure X. The product was purified by flash chromatography using 95:5 methylene chloride:methanol as elutant and TLC prep plate eluted twice with 98:2 methylene chloride:methanol to afford **448** as an off-white solid (0.104 g, 36%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.14 (s, 3H), 4.78 (s, 2H), 7.22 (m, 3H), 7.49 (d, 1H), 7.61 (m, 3H), 7.68 (t, 1H), 8.06 (d, 2H), 8.17 (s, 1H), 9.39 (s, 1H); MS (ES$^-$) *m/z* 482 (M-H)$^-$.

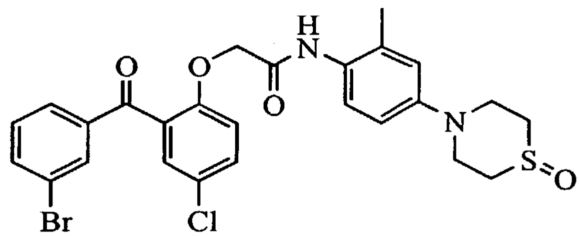
<u>**Example 187**</u>



449

Compound **466** (0.141 g, 0.757 mmol), NEt_3 (0.106 mL, 0.761 mmol), acetonitrile (20 mL total reaction volume), and acid chloride **434** (0.203 g, 0.523 mmol) were used as in general procedure X. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **449** as an off-white solid (0.038 g, 14%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.14 (s, 3H), 4.77 (s, 2H), 7.22 (m, 3H), 7.45 (dd, 2H), 7.6 (m, 4H), 7.72 (d, 1H), 7.82 (d, 1H), 7.88 (s, 1H), 9.3 (s, 1H); MS (ES$^-$) *m/z* 536 (M-H)$^-$.

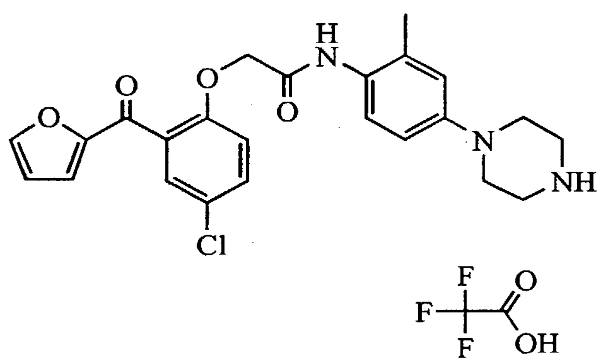
Example 188



450

Compound **399** (1.43 g, 6.37 mmol), NEt_3 (0.888 mL, 6.37 mmol), acetonitrile (50 mL total reaction volume), and acid chloride **434** (1.68 g, 4.64 mmol) were used as in general procedure X. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **450** as an beige solid (1.3 g, 52%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.98 (s, 3H), 2.62 (d, 2H), 2.85 (t, 2H), 3.5 (d, 2H), 3.69 (t, 2H), 4.67 (s, 2H), 6.75 (dd, 1H), 6.82 (d, 1H), 7.08 (d, 1H), 7.2 (d, 1H), 7.42 (d, 1H), 7.46 (d, 1H), 7.62 (dd, 1H), 7.7 (d, 1H), 7.81 (d, 1H), 7.88 (s, 1H), 8.9 (s, 1H); MS (ES$^-$) *m/z* 574 (M-H)$^-$.

Example 189

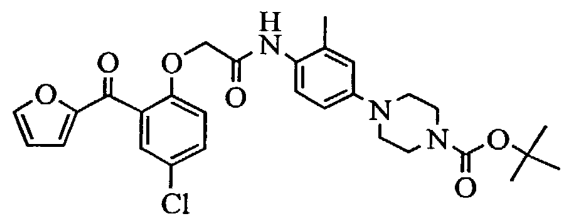


451

Trifluoroacetic acid (TFA, 5 mL, 65 mmol) was added to a solution of compound **452** (0.095 g, 0.17 mmol) in acetonitrile (10 mL) and stirred at rt under nitrogen overnight. Carbon tetrachloride was added to the reaction mixture and the resulting solution was concentrated in vacuo to azeotrope off the TFA. This procedure was repeated multiple times. The product was purified by flash chromatography using 1:1 hexanes:ethyl acetate as elutant to afford **451** as a red/orange solid (0.012 g, 16%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.04 (s, 3H), 3.15 (s, 4H), 3.21 (d, 4H), 4.75 (s, 2H), 6.7 (d, 1H), 6.75 (d, 1H), 6.8

(s, 1H), 7.2 (dd, 2H), 7.3 (d, 1H), 7.5 (d, 1H), 7.58 (d, 1H), 8.06 (s, 2H), 8.19 (bs, 1H), 9.05 (s, 1H); MS (ES$^+$) *m/z* 454 (M+H)$^+$.

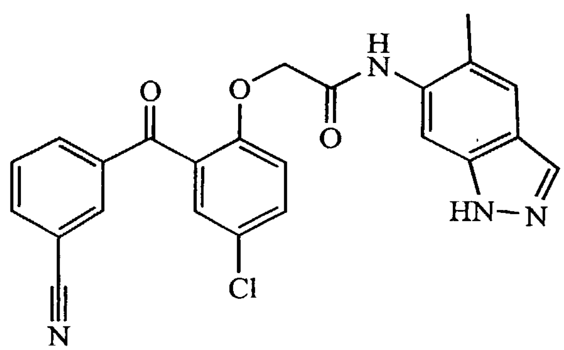
Example 190



452

Compound **367** (0.409 g, 1.4 mmol) in acetonitrile (5 mL total reaction volume), acid chloride **408** (0.3 g, 1 mmol) in acetonitrile, and NEt_3 (0.24 mL, 1.7 mmol) were used as in general procedure X. The product was purified by flash chromatography using 99:1 methylene chloride:methanol as elutant to afford **452** as a brown, viscous oil (0.202 g, 36%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.38 (s, 9H), 2.02 (s, 3H), 3.01 (d, 4H), 3.4 (d, 4H), 4,74 (s, 2H), 6.72 (d, 2H), 6.77 (s, 1H), 7.19 (t, 2H), 7.3 (d, 1H), 7.5 (d, 3H), 7.57 (dd, 1H), 8.05 (s, 1H), 9.01 (s, 1H); MS (ES$^-$) *m/z* 553 (M-H)$^-$.

Example 191

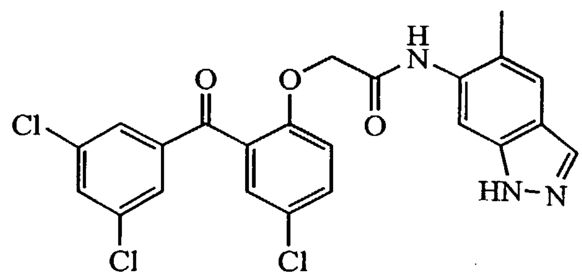


453

Compound **413** (0.072 g, 0.49 mmol) in acetonitrile (10 mL total reaction volume), acid chloride **427** (0.163 g, 0.49 mmol) in acetonitrile, and NEt_3 (0.1 mL, 0.72 mmol) were used as in general procedure X. The product was purified by flash chromatography using 98:2 methylene chloride:methanol as elutant to afford **453** as an off-white solid (0.013 g,

6%). [1]H NMR (DMSO-d_6, 400 MHz) δ 2.16 (s, 3H), 4.77 (s, 2H), 7.25 (d, 1H), 7.5 (s, 2H), 7.65 (m, 3H), 7.89 (s, 1H), 8.08 (d, 2H), 8.16 (s, 1H), 9.03 (s, 1H), 12.84 (s, 1H); MS (ES^-) *m/z* 443 $(M-H)^-$.

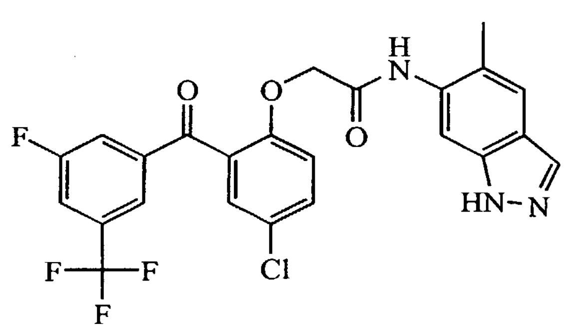
Example 192



454

Carboxylic acid **76** (0.2 g, 0.55 mmol), methylene chloride (CH_2Cl_2, 3 mL), DMF (4 drops), oxalyl chloride (0.13 mL, 1.49 mmol) were used as in general procedure V. The resulting acid chloride was added to a solution of the amine **413** (0.081 g, 0.55 mmol), acetone (5 mL), sodium bicarbonate (0.42 g, 5 mmol), and water (0.5 mL) as used in general procedure VI. The solution was heated to 40°C for 1 h, after which time water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to afford **454** as a gray solid (0.045 g, 17%). [1]H NMR (DMSO-d_6, 300 MHz) δ 2.2 (s, 3H), 4.85 (s, 2H), 7.3 (d, 1H), 7.56 (s, 2H), 7.7 (d, 1H), 7.77 (s, 3H), 7.9 (s, 2H), 9.2 (s, 1H), 12.9 (s, 1H); MS (ES^-) *m/z* 486 $(M-H)^-$.

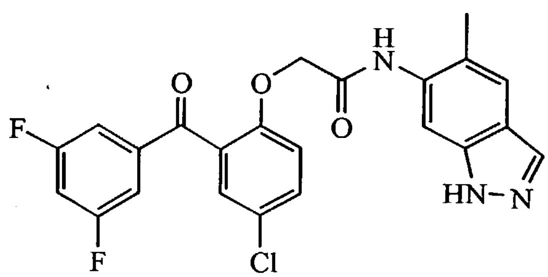
Example 193



455

Carboxylic acid **71** (0.2 g, 0.53 mmol), methylene chloride (3 mL), DMF (4 drops), oxalyl chloride (0.123 mL, 1.41 mmol) were used as in general procedure V. The resulting acid chloride was then added to a solution of the amine **103** (0.078 g, 0.53 mmol), acetone (5 mL), sodium bicarbonate (0.4 g, 4.76 mmol), and water (0.5 mL) as used in general procedure VI. The reaction mixturewas heated to 40°C for 1 h, after which time water (25 mL) was added to the mixture and the resulting suspension was filtered. The solids were washed with ether to afford **455** as a gray solid (0.048 g, 18%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.13 (s, 3H), 4.78 (s, 2H), 7.2 (d, 1H), 7.5 (d, 2H), 7.65 (d, 2H), 7.88 (s, 3H), 7.98 (d, 1H), 9.15 (bs, 1H), 12.8 (bs, 1H); MS (ES$^-$) *m/z* 504 (M-H)$^-$.

Example 194

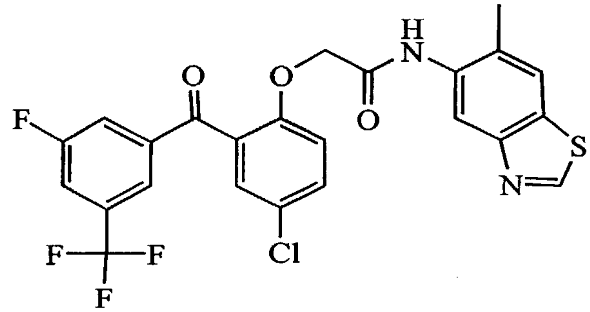


456

Carboxylic acid **49** (0.2 g, 0.6 mmol), methylene chloride (3 mL), DMF (4 drops), oxalyl chloride (0.16 mL, 1.8 mmol) were used as in general procedure V. The resulting acid chloride was then added to a solution of the amine **413** (0.09 g, 0.61 mmol), acetone (10 mL), sodium bicarbonate (0.453 g, 5.4 mmol), and water (0.5 mL) as used in general procedure VI. The reaction mixture was heated to 40 °C for 1 h, after which time water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to give a gray solid. The product was purified by filtering through a silica gel plug eluded with 9:1 hexanes:ethyl acetate. Hexanes were added to the filtrate until a solid formed. The solid was filtered to afford **456** as a white solid (0.034 g, 12%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.2 (s, 3H), 4.85 (s, 2H), 7.3 (d, 1H),

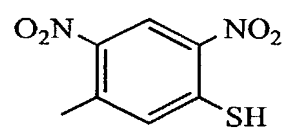
7.5 (d, 2H), 7.56 (d, 2H), 7.62(d, 1H), 7.7 (d, 1H), 7.77 (s, 1H), 7.95 (s, 1H), 9.19 (s, 1H), 12.9 (s, 1H); MS (ES⁻) *m/z* 454 (M-H)⁻.

Example 195



457

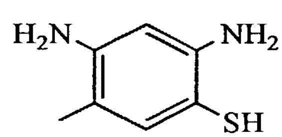
Step A:



458

Sodium sulfide nonahydrate (3.19 g, 13.3 mmol) was added to a solution of 5-fluoro-2,4-dinitrotoluene (Maybridge, 2.47 g, 12.3 mmol) in DMF (20 mL) and the resulting mixture was stirred overnight under nitrogen. Water was added to the reaction and the solution was acidified to pH 2. The suspension was filtered and the solids were washed with 1N HCl to afford **458** as a yellow/orange solid (4.73 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.46 (s, 3H), 7.89 (s, 1H) 8.7 (s, 1H).

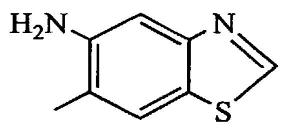
Step B:



459

Compound **458** (2.64 g, 12.3 mmol), palladium on carbon (2 g, 10% w/w), ethanol (200 mL) and THF (100 mL) were used as in general procedure XII to afford **459** as a yellow solid (0.35 g, 18%). The crude material was used without purification.

Step C:



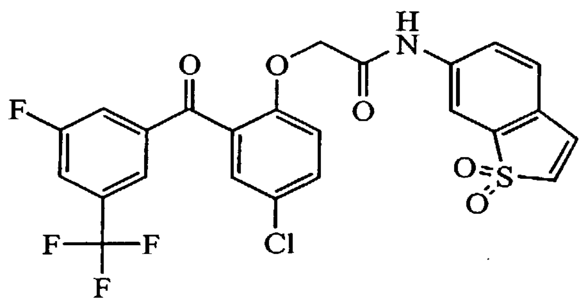
460

Formic acid (96%, 20 mL) was added to compound **459** in a round-bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand. The mixture was refluxed overnight. The mixture was poured into 2N NaOH (200 mL) and the pH was adjusted to 10. The mixture was extracted with ether, dried over $MgSO_4$, and concentrated in vacuo to give an oil. The product was purified by flash chromatography using a gradient between 1:1 hexanes:ethyl acetate and ethyl acetate as elutant to afford **460** as a white solid (0.03g, 8%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.2 (s, 3H), 5.09 (bs, 2H), 7.28 (s, 1H), 7.66 (s, 1H), 9.1 (s, 1H); MS (ES$^+$) *m/z* 165 $(M+H)^+$.

Step D:

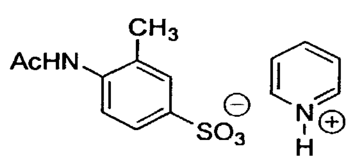
Carboxylic acid **71** (0.091 g, 0.24 mmol), methylene chloride (3 mL), DMF (4 drops), oxalyl chloride (0.057 mL, 0.65 mmol) were used as in general procedure V. The resulting acid chloride was then added to a solution of the amine **460** (0.03 g, 0.18 mmol), acetone (5 mL), sodium bicarbonate (0.18 g, 2.1 mmol), and water (0.5 mL) as used in general procedure VI. The mixture was filtered and the solids were washed with water, ether, and ethyl acetate to afford **457** as an off-white solid (0.064 g, 67%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.18 (s, 3H), 4.79 (s, 2H), 7.25 (d, 1H), 7.54 (d, 1H), 7.65 (dd, 1H), 7.88 (d, 2H), 7.95 (s, 1H), 7.98 (d, 1H), 8.06 (s, 1H), 9.27 (s, 1H), 9.38 (bs, 1H); MS (ES$^-$) *m/z* 521 $(M-H)^-$.

<u>**Example 196**</u>



461

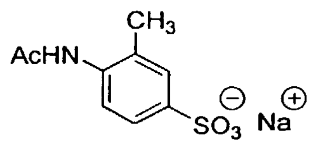
Carboxylic acid **71** (0.091 g, 0.24 mmol), methylene chloride (3 mL), DMF (4 drops), oxalyl chloride (0.057 mL, 0.65 mmol) were used as in general procedure V and added to a solution of 6-amino-1,1-dioxobenzo(b)thiophene (Maybridge, 0.044 g, 0.24 mmol), acetone (10 mL), sodium bicarbonate (0.184 g, 2.2 mmol), and water (1 mL) as used in general procedure VI. The product was purified by filtering through a silica pad eluted with methylene chloride. The organics were washed with saturated sodium bicarbonate, dried over $MgSO_4$, and concentrated in vacuo. The product was further purified by flash chromatography using 9:1 methylene chloride:methanol as elutant to afford **461** as a yellow solid (0.013 g, 10%). ^1H NMR (DMSO-d_6, 400 MHz) δ 4.75 (s, 2H), 7.2 (d, 1H), 7.25 (d, 1H), 7.5 (d, 1H), 7.54-7.58 (m, 2H), 7.59-7.64 (m, 2H), 7.85 (d, 2H), 7.9 (d, 1H), 8 (s, 1H), 10.4 (s, 1H); MS (ES$^-$) *m/z* 538 (M-H)$^-$.



462

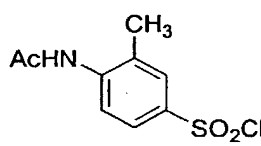
Into a round-bottom flask were placed 2-aminotoluene-5-sulfonic acid (50.0 g, 267 mmol), and pyridine (300 mL). Acetic anhydride (38 mL, 403 mmol) was added dropwise from an addition funnel and the resulting mixture was allowed to stir for 2 h at rt. The solvents were removed under reduced pressure, to leave a brown solid. Several portions of ethyl alcohol were added to the solid and subsequently removed under reduced pressure, to afford a brown solid which was filtered and washed with several additional portions of ethyl alcohol and dried under vacuum (67.03 g, 81%) ^1H NMR (DMSO-d_6,) δ 2.08 (s,

3H), 2.22 (s, 3H), 7.39 (s, 2H), 7.45 (s, 1H), 8.02 (t, J= 6 Hz, 2H), 8.53 (t, J= 6Hz, 1H), 8.92 (d, J= 6Hz, 2H), 9.31 (s, 1H).



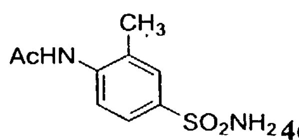
463

Compound **462** (67.03 g, 217 mmol) was added to a round-bottom flask containing 1N NaOH (225 mL) and the resulting mixture was allowed to stir at rt for 3 h. The mixture was concentrated under reduced pressure, to afford a brown solid. Several portions of ethyl alcohol were added and subsequently removed under reduced pressure. The remaining solid was filtered, washed with a final portion of ethyl alcohol and dried under vacuum (42.34 g, 77%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.08 (s, 3H), 2.22 (s, 3H), 7.39 (s, 2H), 7.45 (s, 1H), 9.31 (s, 1H).



464

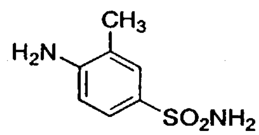
Sulfonic acid salt **463** (42.34 g, 169 mmol) and DMF (300 mL) were added to a flask that was equipped with a stir bar and nitrogen on demand and was cooled to 0 °C. Thionyl chloride (30 mL, 411 mmol) was added dropwise from an addition funnel at a rate such that the temperature of the reaction mixture did not exceed 10 °C. When the addition was complete, the mixture was allowed to warm to rt and stir for an additional 2 1/2 h, after which time it was poured into a beaker containing crushed ice. The resulting solid was collected by filtration, washed with several portions of water and dried under vacuum (25.63 g, 61%). ^{1}H NMR (DMSO, d_6, 400 MHz) δ 2.02 (s, 3H), 2.15 (s, 3H), 7.33 (s, 2H), 7.38 (s, 1H), 9.27 (s, 1H).



465

Into a round-bottom flask, equipped with a stir bar and nitrogen on demand, were placed sodium acetate (19.82 g, 241.6 mmol) and ethyl alcohol (200 mL) and the mixture was

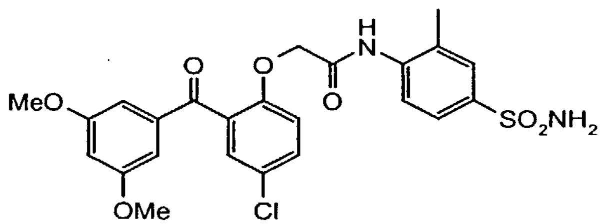
cooled to 0 °C. Ammonia gas was bubbled through the sodium acetate solution for 5 min, then sulfonyl chloride **464** (25.63 g, 103 mmol) was added as a solid and in one portion. The resulting mixture was allowed to stir at 0 °C for 30 min, and was then allowed to warm to rt and stir for an additional 18 h. The mixture was then diluted with water and was poured into a separatory funnel containing water and ethyl acetate. The organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to provide **465** as a yellow solid (8.4 g, 36%), which was used without further purification.



466

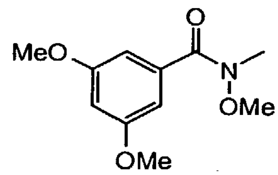
A round-bottom flask was equipped with a stir bar, a reflux condenser and nitrogen on demand. Into the flask were placed sulfonamide **465** (8.4 g, 36.80 mmol), ethyl alcohol (200 mL) and 2N hydrochloric acid (128 mL). The resulting mixture was allowed to heat to reflux overnight, after which time it was allowed to cool to RT and was neutralized with saturated, aqueous sodium bicarbonate. It was then poured into a separatory funnel containing water and ethyl acetate, the organic layer was collected, washed with water, brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford a tan solid (6.35 g, 93%), which was used without further purification. ^1H NMR (DMSO-d_6, 400 MHz) δ 2.06 (s, 3H), 5.54 (s, 2H), 6.58 (d, J= 12 Hz, 1H), 6.82 (s, 2H), 7.30 (d, J= 12 Hz, 1H), 7.33 (s, 1H).

<u>**Example 197:**</u>



467

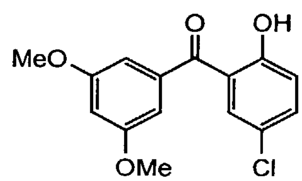
Step A:



468

The title compound was prepared according to General Procedure VII from 3,5-dimethoxybenzoyl chloride (2.00 g, 10.0 mmol). The reaction gave **468** as a colorless oil (2.143 g, 95%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.75 (d, 2 H), 6.49 (t, 1 H), 3.76 (s, 6 H), 3.55 (s, 3 H), 3.29 (s, 3 H).

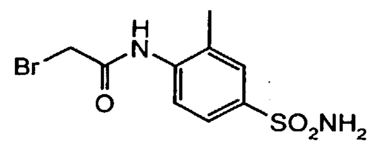
Step B:



469

A solution of 2-bromo-4-chlorophenol (0.830 g, 4.0 mmol) in 20 mL of THF was cooled to –78 °C in a dry ice/acetone bath. *n*-Butyllithium (5.5 mL of a 1.6 M solution in hexanes, 8.8 mmol) was added dropwise over 5 min, and the resulting mixture was stirred at –78 °C for 1 h. A solution of **468** (0.901 g, 4.0 mmol) in 5 mL of THF was added dropwise over 4 min, and the resulting mixture was stirred at –78 °C for 1.25 h, then at room temperature for 14 h. The reaction mixture was poured into 50 mL of water and extracted with two 50-mL portions of EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1.193 g of a brown oil. Purification by flash chromatography using 10% EtOAc/hexanes as an eluant followed by crystallization from hot ether gave **469** as yellow crystals (0.234 g, 20%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.83 (s, 1 H), 7.62 (d, 1 H), 7.45 (dd, 1 H), 7.03 (d, 1 H), 6.76 (d, 2 H), 6.68 (t, 1 H), 3.84 (s, 6 H).

Step C:



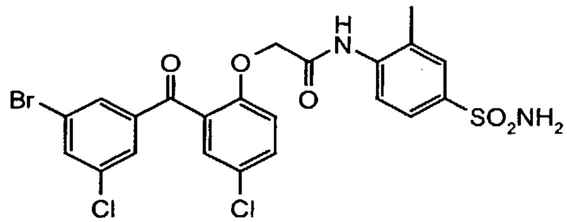
470

A solution of **466** (5.0 g, 26.85 mol) and pyridine (2.4 mL, 29.53 mmol) in 150 mL of chloroform was cooled to 0 °C in an ice bath. Bromoacetyl bromide (2.6 mL, 29.53 mmol) was added dropwise over 20 min, and the resulting mixture was allowed to slowly warm to room temperature as it was stirred for 18 h. The reaction mixture was then poured into 150 mL of water and extracted with two 100-mL portions of CH_2Cl_2. Both the organic and aqueous layers were filtered to yield a beige solid. This solid was suspended in 40 mL of 1 N HCl and stirred several minutes. The solid was then filtered and rinsed with CH_2Cl_2, MeOH, and hexanes to yield **470** (5.705 g, 69%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.84 (s, 1H), 7.66-7.56 (m, 3 H), 7.23 (br s, 2 H), 4.09 (s, 2 H), 2.24 (s, 3 H).

Step D:

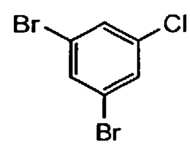
A mixture of **469** (0.144 g, 0.49 mmol), **470** (0.162 g, 0.53 mmol), and potassium carbonate (0.339 g, 2.45 mmol) in 5 mL of acetone was warmed to reflux for 6 h, then stirred at room temperature overnight. The reaction mixture went dry overnight, so another 5 mL of acetone was added, and the resulting mixture was heated to reflux for 8 h, then stirred at room temperature for 22 h. The reaction mixture was poured into 30 mL of water and extracted with two 30-mL portions of EtOAc. The combined organic layers were filtered to remove solid, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.195 g of a yellow solid. Purification by suspension in hot ether followed by filtration gave **467** (0.094 g, 37%): MS (AP+) *m/z* 518.9 (M+H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.15 (s, 1H), 7.63-7.60 (m, 3 H), 7.56 (dd, 1 H), 7.39 (d, 1 H), 7.22 (s, 2H), 7.18 (d, 1 H), 6.82 (d, 2 H), 6.71 (t, 1 H), 4.76 (s, 2 H), 3.69 (s, 6 H), 2.12 (s, 3 H).

Example 198:



471

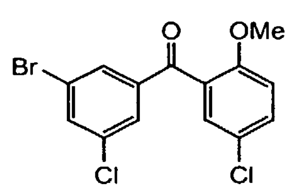
Step A:



472

A solution of 1,3,5-tribromobenzene (9.44 g, 30 mmol) in 120 mL of ether was cooled to –78 °C in a dry ice/acetone bath. *n*-Butyllithium (13.2 mL of 2.5 M solution in hexanes, 33 mmol) was added dropwise over 10 min. The resulting mixture was stirred at –78 °C for an additional 10 min, then hexachloroethane (7.15 g, 30.2 mmol) was added in small portions over 3 min. The reaction mixture was then stirred for 15 min at –78 °C, followed by 3.2 h at rt. The mixture was partitioned between 100 mL of water and 100 mL of EtOAc. The aqueous layer was separated and extracted with an additional 100 mL of EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give **472** as a pale brown solid (7.72 g, 95%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 (t, 1 H), 7.47 (d, 2 H).

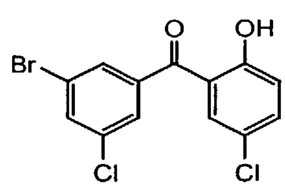
Step B:



473

A solution of **472** (7.62 g, 28.2 mmol) in 100 mL of ether was cooled to –78 °C in a dry ice/acetone bath. *n*-Butyllithium (12.6 mL of 2.5 M solution in hexanes, 31.5 mmol) was added dropwise over 30 min. The resulting mixture was stirred at –78 °C for an additional 13 min, then **183** (6.57 g, 28.6 mmol) was added in small portions over 23 min. The reaction mixture was then stirred for 22 h as the bath was allowed to warm to room temperature. The mixture was poured into 100 mL water and extracted with two 100-mL portions of EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 9.46 g of a beige solid. Recrystallization from hot MeOH gave **473** (6.45 g, 64%): MS (AP-) *m/z* 358 (M-H); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (t, 1 H), 7.70 (t, 1 H), 7.65 (t, 1 H), 7.47 (dd, 1 H), 7.36(d, 1 H), 6.95 (d, 1 H), 3.72 (s, 3 H).

Step C:



474

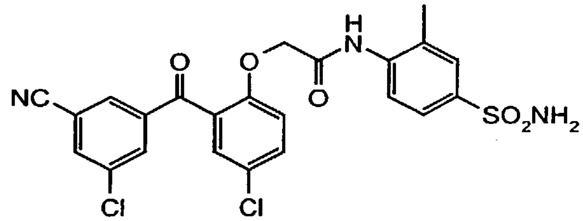
The title compound was prepared according to General Procedure IX from **473** (0.338 g, 0.94 mmol). The reaction gave **474** (0.325 g, 100%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.54 (s, 1 H), 7.72 (t, 1 H), 7.62 (d, 1 H), 7.52 (d, 1 H), 7.46 (dd, 1 H), 7.41 (d, 1 H), 7.02 (d, 1 H).

Step D:

A mixture of **474** (0.173 g, 0.50 mmol), **470** (0.154 g, 0.50 mmol), and potassium carbonate (0.346 g, 2.5 mmol) in 10 mL of acetone was warmed to reflux for 15 h and stirred at room temperature another 4 h. The reaction mixture was then poured into 35 mL of water and extracted with two 35-mL portions of EtOAc. The aqueous layer was then filtered and extracted with another 20 mL of EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.230 g

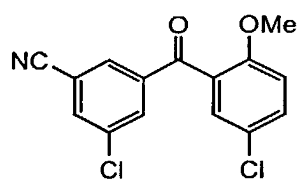
of a yellow oil. Purification by flash chromatography using 0.5-1% $MeOH/CH_2Cl_2$ gave **471** (0.048 g, 17%): MS (AP+) *m/z* 573 (M+H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.36 (s, 1 H), 7.97 (t, 1 H), 7.79 (s, 1 H), 7.71 (s, 1 H), 7.68-7.47 (m, 4 H), 7.45 (d, 1 H), 7.21 (s, 2 H), 7.20-7.18 (d, 1 H), 4.77 (s, 2 H), 2.13 (s, 3 H).

Example 199:



475

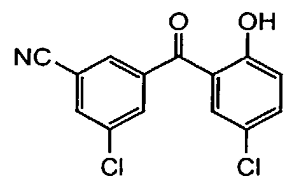
Step A:



476

A solution of **473** (0.299 g, 0.83 mmol), sodium cyanide (0.086 g, 1.76 mmol), copper (I) iodide (0.028 g, 0.15 mmol), and tetrakis-(triphenylphosphine)-palladium (0.113 g, 0.10 mmol) in 8 mL of acetonotrile was heated to reflux for 40 min. The reaction mixture was then diluted with 50 mL of EtOAc and filtered through Celite. The resulting solution was washed with 25 mL of water, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 0.375 g of an orange gum. Purification by flash chromatography using 5% EtOAc/hexane as the eluant gave **476** (0.171 g, 56%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (t, 1H), 7.82 (t, 1 H), 7.76 (t, 1 H), 7.47 (dd, 1 H), 7.37 (d, 1 H), 6.93 (d, 1 H), 3.67 (s, 3 H).

Step B:



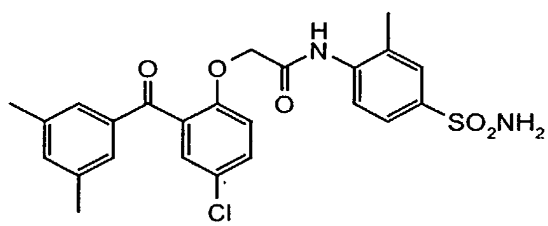
477

The title compound was prepared according to General Procedure IX from **476** (0.165 g, 0.54 mmol). The reaction gave **477** (0.174 g, 100%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.43 (s, 1 H), 7.84-7.82 (m, 2 H), 7.78 (t, 1 H), 7.49 (dd, 1 H), 7.34 (d, 1 H), 7.05 (d, 1 H).

Step C:

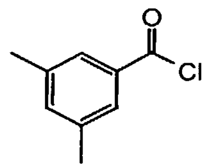
A mixture of **477** (0.157 g, 0.54 mmol), **470** (0.165 g, 0.54 mmol), and potassium carbonate (0.373 g, 2.7 mmol) in 10 mL of acetone was warmed to reflux for 17.5 h. The reaction mixture was then poured into 35 mL of water and extracted with two 35-mL portions of EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.276 g of a yellow oil. Purification by flash chromatography using 0.5-1% MeOH/CH_2Cl_2 gave **475** (0.033 g, 12%): MS (AP-) *m/z* 517 (M-H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.42 (s, 1 H), 8.26 (s, 1 H), 8.11 (s, 1 H), 8.03 (t, 1 H), 7.63 (dd, 1 H), 7.60-7.53 (m, 3 H), 7.49 (d, 1 H), 7.22 (s, 2 H), 7.19 (d, 1H), 4.77 (s, 2 H), 2.14 (s, 3 H).

Example 200:



478

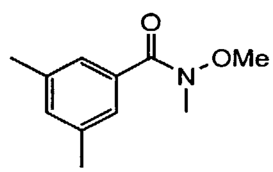
Step A:



479

The title compound was prepared according to General Procedure V from 3,5-dimethylbenzoic acid (1.50 g, 10.0 mmol). The reaction work-up gave **479** (2.214 g), which was used immediately without purification.

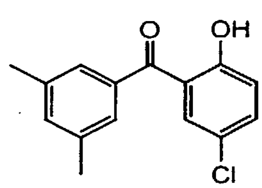
Step B:



480

The title compound was prepared according to General Procedure VII from **479** (2.214 g). The reaction workup gave **480** as a yellow oil (2.073 g, 100%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (s, 2 H), 7.07 (s, 1 H), 3.57 (s, 3 H), 3.33 (s, 3 H), 2.33 (s, 6 H).

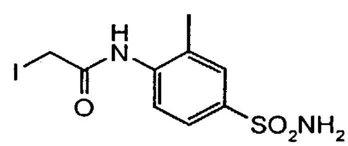
Step C:



481

A solution of 2-bromo-4-chlorophenol (0.844 g, 4.07 mmol) in THF (20 mL) was cooled to –78 °C in a dry ice/acetone bath. *n*-Butyllithium (5.6 mL of 1.6 M solution in hexanes, 8.95 mmol) was added dropwise over 6 min, and the resulting mixture was stirred at –78 °C for 1 h. A solution of **480** (0.786 g, 4.07 mmol) in 5 mL of THF was added dropwise over 6 min, and the resulting mixture was stirred at –78 °C for 1.25 h and at room temperature for 14 h. The reaction mixture was then poured into 50 mL of water and extracted with two 50-mL portions of EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1.014 g of a brown solid. Purification by flash chromatography using 5% EtOAc/hexanes as an eluant followed by crystallization from hot ether gave **481** as yellow crystals (0.296 g, 28%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.94 (s, 1 H), 7.57 (d, 1 H), 7.44 (dd, 1 H), 7.25 (s, 3 H), 7.03 (d, 1 H), 2.40 (s, 6 H).

Step D:



482

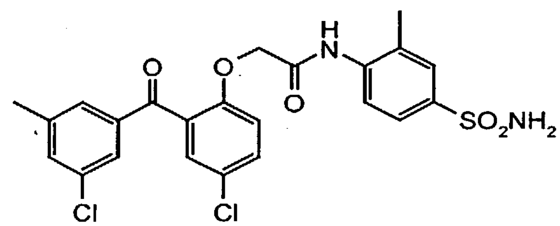
A mixture of **470** (1.27 g, 3.53 mmol) and sodium iodide (1.61 g, 10.7 mmol) in 10 mL of acetone was stirred at room temperature for 20.5 h. The reaction mixture was then diluted with 60 mL of water and 60 mL of CH_2Cl_2 and stirred for another 20 min. Filtration of the mixture then gave **482** as a beige solid (1.197 g, 96%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.81 (s, 1 H), 7.65-7.61 (m, 3 H), 7.26 (s, 2 H), 3.90 (s, 2 H), 2.28 (s, 3 H).

Step E:

A mixture of **481** (0.130 g, 0.5 mmol), **482** (0.195 g, 0.55 mmol), and potassium carbonate (0.156 g, 1.13 mmol) in 5 mL of acetone was warmed to reflux for 8 h, then stirred at room temperature an additional 12 h. The reaction mixture was then partitioned between 30 mL of water and 30 mL of EtOAc. The aqueous layer was separated and extracted

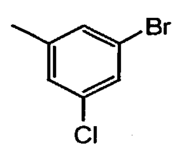
with two 30-mL portions of CH_2Cl_2. All layers were filtered to give 0.172 g of an off-white solid. This solid was suspended in 200 mL of hot acetone and filtered again to give 0.116 g of a yellow solid. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.117 g of a second yellow solid. The two yellow solids were combined and purified by flash chromatography using 0.5-1% $MeOH/CH_2Cl_2$ to give **478** as a white solid (0.108 g, 44%): MS (AP+) *m/z* 487 (M+H); ^1H NMR (DMSO-d_6, 400 MHz) δ 9.08 (s, 1 H), 7.63-7.54 (m, 4 H), 7.36 (s, 3 H), 7.22-7.18 (m, 4 H), 4.75 (s, 2 H), 2.22 (s, 6 H), 2.10 (s, 3 H).

<u>Example 201:</u>



483

Step A:

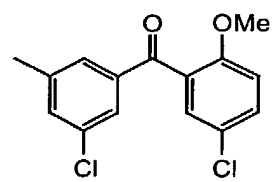


484

A solution of 3,5-dibromotoluene (1.25 g, 5.0 mmol) in 25 mL of ether was cooled to –78 °C in a dry ice/acetone bath. *n*-Butyllithium (2.2 mL of 2.5 M solution in hexanes, 5.5 mmol) was added dropwise over 3 min. The resulting mixture was stirred at –78 °C for an additional 11 min, then hexachloroethane (1.18 g, 5.0 mmol) was added in small portions over 4 min. The reaction mixture was then stirred for 14 min at –78 °C, followed by 17 h at room temperature. The reaction mixture was poured into 50 mL of water and extracted with two 50-mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give **484** as a light brown solid (0.885 g,

86%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 1 H), 7.22 (s, 1 H), 7.10 (s, 1 H), 2.31 (s, 3 H).

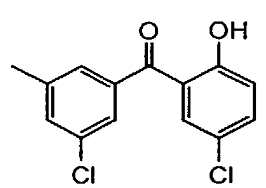
Step B:



485

A solution of **484** (0.875 g, 4.26 mmol) in 24 mL of ether was cooled to –78 °C in a dry ice/acetone bath. *n*-Butyllithium (2.1 mL of 2.5 M solution in hexanes, 5.25 mmol) was added dropwise over 5 min. The resulting mixture was stirred at –78 °C for an additional 15 min, then **183** (0.978 g, 4.26 mmol) was added in small portions over 6 min. The reaction mixture was then stirred for 26 h as the bath was allowed to warm to room temperature. The reaction mixture was poured into 25 mL water and extracted with 50 mL of CH_2Cl_2. The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 1.224 g of a brown solid. Recrystallization from hot ether gave **485** (0.536 g, 43%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (s, 1 H), 7.45 (s, 1 H), 7.40 (dd, 1 H), 7.33 (d, 1 H), 7.28 (d, 1 H), 6.90 (d, 1 H), 3.68 (s, 3 H), 2.34 (s, 3 H).

Step C:



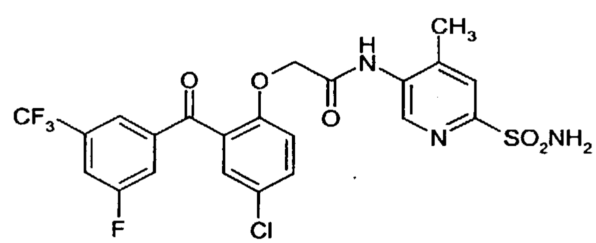
486

The title compound was prepared according to General Procedure IX from **485** (0.295 g, 1.0 mmol). The reaction gave **486** (0.285 g, 100%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.71 (s, 1 H), 7.46 (d, 1 H), 7.43 (dd, 1 H), 7.39 (s, 1 H), 7.38 (s, 1 H), 7.29 (s, 1 H), 7.00 (d, 1 H), 2.40 (s, 3 H).

Step D:

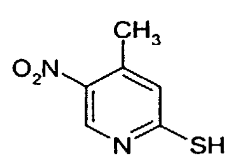
A mixture of **486** (0.141 g, 0.5 mmol), **482** (0.195 g, 0.55 mmol), and potassium carbonate (0.138 g, 1.0 mmol) in 10 mL of acetone was warmed to reflux for 8 h, then stirred at room temperature an additional 8 h. The reaction mixture was poured into 30 mL of water and extracted with 30 mL of EtOAc and 30 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.238 g of crude material. Purification by flash chromatography using 0.5-2% $MeOH/CH_2Cl_2$ to give **483** as a white solid (0.111 g, 44%): ^1H NMR (DMSO-d_6, 400 MHz) δ 9.23 (br s, 1 H), 7.62-7.54 (m, 4 H), 7.51 (s, 2 H), 7.49 (s, 1 H), 7.42 (d, 1 H), 7.21 (br s, 2 H), 7.19 (d, 1 H), 4.76 (s, 2 H), 2.27 (s, 3 H), 2.12 (s, 3 H).

Example 202:



487

Step A:

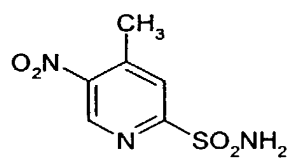


488

To a heat-dried, 3-necked, round bottom flask equipped with a nitrogen inlet and reflux condenser was added 2-chloro-4-methyl-5-nitropyridine (Aldrich Chemical Co., 4.12 g,

23.9 mmol), thiourea (1.82 g, 23.9 mmol), and ethanol (40 ml). The mixture was warmed to reflux whereupon components dissolved, and the solution stirred for 3 h at reflux. A yellow precipitate was observed after 2 h. A solution of potassium hydroxide (2.01 g, 35.9 mmol) in water (8 mL) was added and the mixture was heated for an additional 1 h. The reaction mixture was allowed to cool to rt, and was diluted with 1M sodium hydroxide (150 mL). This mixture was extracted with methylene chloride (75 mL), and the pH of the aqueous layer adjusted from 12 to 7 with glacial acetic acid. The resulting solid was filtered and dried in vacuo to yield **488** (2.36 g, 58%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.47 (s, 1H), 7.25 (s, 1H), 2.39 (s, 3H).

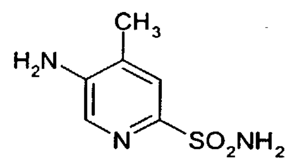
Step B:



489

488 (850 mg, 5 mmol) was suspended in 1N hydrochloric acid (13 ml) and cooled to 0 °C. Chlorine gas was bubbled through the suspension for 30 min, at a rate that allowed the reaction to remain near 0 °C. The reaction mix was stirred for 15 min further at 0 °C after gas introduction was stopped. Chloroform (30 ml) was added to the mixture and stirred at 0 °C until the solids dissolved. The layers were partitioned, the aqueous layer extracted with chloroform (10 mL), and the organic layers were combined, placed in a 100 ml round bottom flask and cooled in an ice/water bath. Ammonia liquid (~5 mL) was added to the solution via a cold finger trap cooled to –78 °C (CO_2/acetone). A precipitate formed and the mixture and was allowed to warm to 0 °C and for 5 min, followed by 1 h at rt. The mixture was then heated to 45 °C and concentrated in vacuo to a provide a yellow solid which was washed with ether and dried to give **489** (856 mg, 79%) as a tan solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.25 (s, 1H), 8.13 (s, 1H), 2.69 (s, 3H); MS (AP-): m/z 217 (M^-).

Step C:



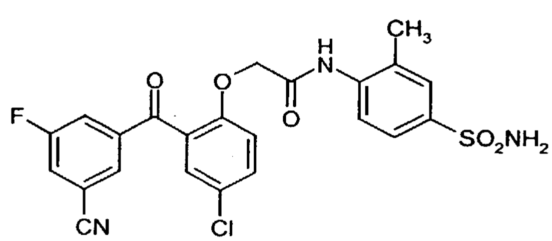
490

489 (2.36 g, 10.88 mmol) was treated according to General Procedure XII to give **490** (2.05 g, >99%), which was used without further purification.

StepD:

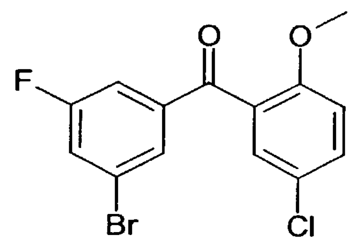
Acid **71** (200 mg, 0.53 mmol) was treated according to general procedure V. The product obtained was then allowed to react with **490** (0.53 mmol) according to general procedure VI. The resulting product was purified by silica gel chromatography (5% MeOH/CH_2Cl_2) followed by recrystallization from acetonitrile/water, to give **487** (27 mg, 9%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.7 (s, 1H), 8.61 (s, 1H), 7.97 (d, J = 8.4, 1H), 7.85 (m, 2H), 7.76 (s, 1H), 7.63 (dd, J = 9, 2.8, 1H), 7.51 (d, J = 2.7, 1H), 7.34 (s, 1H), 7.21 (d, J = 9.2, 1H), 4.80 (s, 2H), 2.17 (s, 3H); MS (ES+): m/z 546 (M^+).

<u>**Example 203**</u>



491

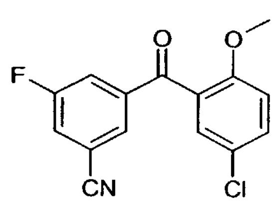
Step A:



492

Into a two-neck flask equipped with a nitrogen inlet was placed 3,5-dibromofluorobenzene (1.12 g, 4.4 mmol) and anhydrous ether (8 mL). This solution was cooled to –78 °C (CO_2/acetone) and n-butyllithium (2.5M in hexanes, 1.92 ml, 4.8 mmol) was added dropwise. The resulting solution was stirred at –78 °C for 10 min, after which time a solution of *N*-methyl-*N*-methoxy-2-methoxy-5-chlorobenzamide (1 g, 4.37 mmol) in ether (40 mL) was added dropwise. The cooling bath was removed and the reaction was allowed to warm to rt, stir for an additional for 1 h, followed by the addition of 1M H_3PO_4 (50 mL). The mixture was stirred for 30 min, and the layers were separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The product was then triturated with methanol to give **492** (0.63 mg, 42%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (s, 1H), 7.53 – 7.39 (m, 4H), 6.99 (d, *J* = 8.9, 1H), 3.76 (s, 3H).

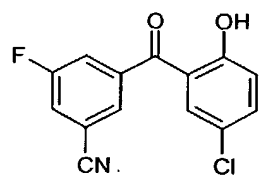
Step B:



493

492 (1.3 g, 3.8 mmol) was treated according to General Procedure XV to give **493** (1.09 g, >99%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (s, 1H), 7.78 (d, *J* = 8.7, 1H), 7.60 – 7.53 (m, 2H), 7.44 (d, *J* = 2.6, 1H), 7.00 (d, *J* = 8.8, 1H), 3.75 (s, 3H); MS(EI+): *m/z* 289 (M^+).

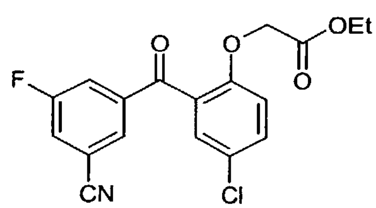
Step C:



494

493 was treated according to the procedure used for the synthesis of compound **4** to give **494** (1.09 g, >99%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.51 (s, 1H), 7.79 (s, 1H), 7.67 (d, *J* = 7.8, 2H), 7.57 (dd, *J* = 9.0, 2.4, 1H), 7.44 (d, *J* = 2.4, 1H), 7.13 (d, *J* = 9.0, 1H); MS(ES-): *m/z* 274 $(M-H)^-$.

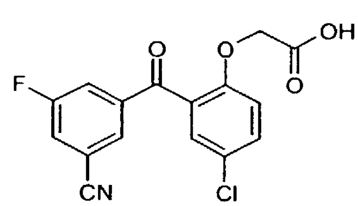
Step D:



495

494 was treated according to General Procedure II. The product was purified by silica gel chromatography (20% ethyl acetate/hexanes) to afford **495** (1.27 g, 89%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (s, 1H), 7.80-7.78 (m, 1H), 7.50 – 7.42 (m, 3H), 6.76 (d, *J* = 8.6, 1H), 4.49 (s, 2H), 4.18 (q, *J* = 14.2, 7.1, 2H), 1.21 (t, *J* = 3.5, 3H).

Step E:



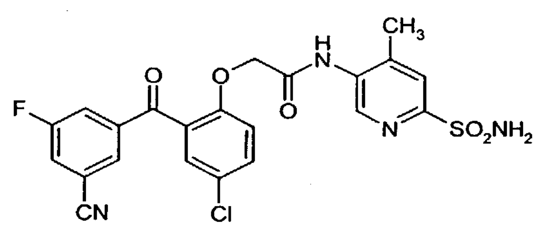
496

495 was treated according to General Procedure III to give **496** (1.0 g, 85%) as a white solid which was used without further purification. [1]H NMR (DMSO-d_6, 400MHz) δ 8.09 (d, J = 7.9, 1H), 8.00 (s 1H), 7.90 (d, J = 8.8, 1H), 7.55 (dd, J = 8.9, 2.5, 1H), 7.43 (d, J = 2.6, 1H), 7.03 (d, J = 9.0 2H); MS(ES-): m/z 332 $(M\text{-}H)^-$.

Step F:

496 was used according to General Procedure V, and was further allowed to react with compound **466** according to General Procedure VI, to afford **491** (290 mg, 58%) as a white solid. [1]H NMR (DMSO-d_6, 400MHz) δ 9.43 (s, 1H), 8.1 (d, J = 8.2, 1H), 8.02 (s, 1H), 7.88 (d, J = 9.0, 1H), 7.64 – 7.48 (m, 5H), 7.22 – 7.17 (m, 3H), 4.77 (s, 2H), 2.14 (s, 3H); MS(ES-): m/z 500 $(M\text{-}H)^-$. Anal. Calcd for $C_{23}H_{17}N_3O_5ClFS$: C, 55.04; H, 3.41; N, 8.37. Found: C, 55.07; H, 3.56; N, 8.35.

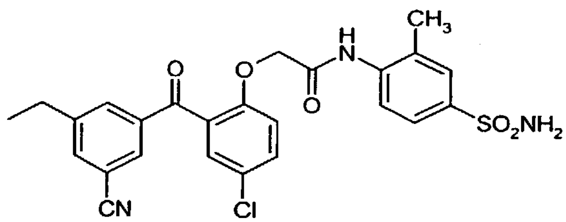
Example 204:



497

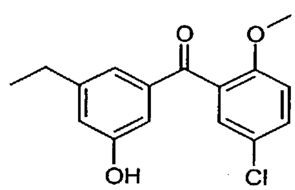
496 was treated according to general procedure V, and was then further allowed to react with **490** according to general procedure VI. The product was purified by silica gel chromatography (5% methanol/methylene chloride), followed and by washing with ethyl acetate/hexanes to afford **497** (48 mg, 19%). [1]H NMR (DMSO-d_6, 400MHz) δ 9.73 (s, 1H), 8.64 (s, 1H), 8.10 (d, J = 8.1, 1H), 8.02 (s, 1H), 7.88 (d, J = 8.8, 1H), 7.76 (s, 1H), 7.62 (dd, J = 8.9, 2.7, 1H), 7.49 (d, J = 2.5, 1H), 7.35 (s, 2H), 4.81 (s, 2H), 2.20 (s, 3H). MS(ES-): m/z 501 $(M\text{-}H)^-$. Anal. Calcd for $C_{22}H_{16}N_4O_5ClFS$: C, 52.54; H, 3.21; N, 11.14. Found: C, 52.30; H, 3.34; N, 10.96.

Example 205:



498

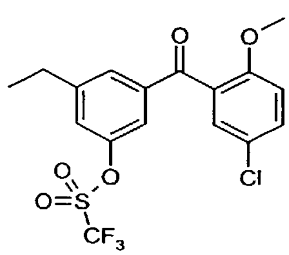
Step A:



499

2-bromo-4-ethylphenol (prepared according to the procedure of Sargent et al. in *J. Chem. Soc. Perkin Trans. 1*, **1984,** 1621), and *N*-methyl-*N*-methoxy-2-methoxy-5-chlorobenzamide were treated according to the procedures outlined by Selnick et al. in *Tetrahedron Lett.* **1993,** *34*, 2043-2046 to give **499** (185 mg, 11%). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.37 (dd, *J* = 8.7, 2.5, 1H), 7.32 – 7.22 (m, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 6.98 – 6.84 (m, 2H), 5.16 (bs, 1H), 3.69 (s, 3H), 2.59 (q, *J* = 15.2, 7.5, 2H), 1.18 (t, *J* = 7.6, 3H).

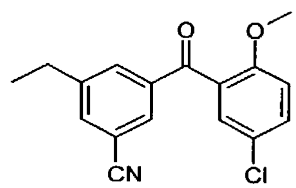
Step B:



500

499 (185 mg, 0.64 mmol) was dissolved in DMF (2 mL) and treated with sodium hydride (31 mg 60% dispersion in oil, 0.8 mmol)and the resulting mixture was stirred for 30 min until bubbling ceased. N-phenyltriflimide (286 mg, 0.8 mmol) was added in one portion. The mixture was stirred for 3 h, then partitioned between ether and water (50 mL each). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give **500** (256 mg, 95%) which was used without purification. MS(ES+): *m/z* 423 ($M+H^+$).

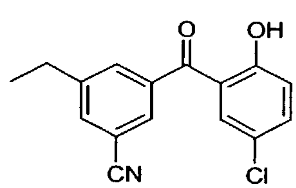
Step C:



501

500 (256 mg, 0.61 mmol) was treated as described in General Procedure XV to give a crude product which was purified by silica gel chromatography (20% ethyl acetate/hexanes) to give **501** (158 mg, 87%). ^1H NMR ($CDCl_3$, 400MHz) δ 7.85 (s,1H), 7.74 (s, 1H), 7.63 (s, 1H), 7.44 (dd, J = 8.9, 2.6, 1H), 7.33 (d, J = 2.7, 1H), 6.91 (d, J = 8.8, 1H), 3.66 (s, 3H), 2.71 (q, J = 15.2, 7.5, 2H), 1.24 (t, J = 7.6, 3H).

Step D:



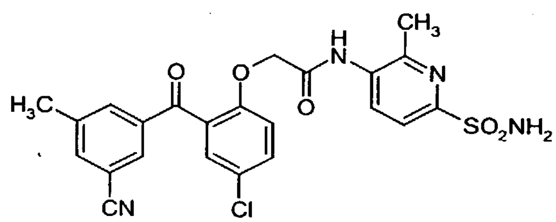
502

501 (158 mg, 0.53 mmol) was treated according to the procedure for the synthesis of compound 4 to give **502** (152 mg, >99%) as a yellow solid, which used without further purification. MS(ES-): *m/z* 284 $(M-H)^-$.

Step E:

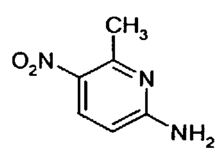
502 (152 mg, 0.53 mmol) and **470** were treated according to the procedure for the synthesis of **467** to give a crude product which was triturated with 10% methanol/ether to give **498** (100 mg, 37%). ^{1}H NMR (DMSO-d_6, 300MHz) δ 9.42 (s, 1H), 8.03 – 7.99 (m, 2H), 7.69-7.61 (m, 4H), 7.54 (d, J = 2.6, 1H), 4.84 (s, 2H), 2.72 (q, J = 15.1, 7.6, 2H), 2.20 (s, 3H), 1.19 (t, J = 7.5, 3H); MS(ES-): m/z 284 (M-H)$^-$.

Example 206:



503

Step A:

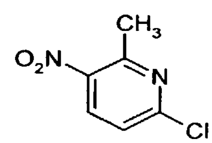


504

Concentrated sulfuric acid (200 mL) was cooled to 5 °C and 6-methyl-2-pyridinamine (50g, 0.46 mol, Aldrich Chemical Co.) was added over 20 min. while the reaction temperature was maintained below 50 °C. Fuming nitric acid (30 mL) was then added slowly over 30-40 min. and the resulting mixture was allowed to warm to rt and stand for approximately 1 h. The reaction was then heated to 55 °C for 1 h, then poured carefully into a mixture of 5N sodium hydroxide (1L) and ice. The final pH was adjusted to 10 with 5N and then 1N sodium hydroxide and the product precipitated as a mixture of the 6-methyl- 4 and 5-nitro-2-pyridinamines in 75% yield. A pure sample of **504** was provided by sublimation. GCMS (EI $^+$) 153 m/z. ^{1}H NMR (DMSO-d_6) δ 8.2 (d, IH, Ar), 7.9

(bs,2H,NH_2), 6.6 (d, 1H, Ar), 2.4 (s,3H, CH_3). The structure was confirmed by a heteronuclear multiple bond coherence experiment (HMBC). A proton on the 6-methyl group exhibited a three bond coupling with the 5-carbon atom bearing the nitro group.

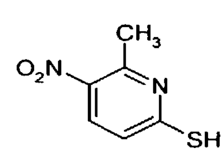
Step B:



505

A mixture of 504 and 6-methyl-4-nitro-2-pyridinamines (0.5g, 3.3 mmol) was stirred with carbon tetrachloride (15 mL). Trimethylsilyl chloride in dichloromethane (1M, 10 mL, 10 mmol) was added and the reaction heated in a 70 °C oil bath for 30 min. Trimethylsilyl chloride (0.5 mL, 4 mmol) was added the reaction was heated another 30 min. t-Butyl nitrite (4 mL, 30 mmol, 10 eq.) was added and the reaction was heated to reflux overnight. The reaction was filtered and the solvents removed in vacuo. **505** was isolated by chromatography on a 4 X 15 cM column of silica gel eluted with hexane/ethyl acetate (6:1, 1 L). GCMS (CI^+) 173 m+1/z. ^{1}H NMR ($CDCl_3$) δ 8.2 (d, IH, Ar), 7.3 (d, 1H, Ar), 2.8 (s, 3H, CH_3). The structure was confirmed by a heteronuclear multiple bond coherence experiment (HMBC). A proton on the 6-methyl group exhibited a three bond coupling with the 5-carbon atom bearing the nitro group.

Step C:

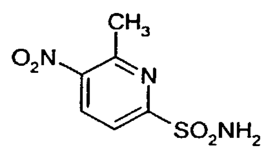


506

505 (0.4 g, 2.4 mmol) was dissolved in ethanol (30 mL). Thiourea (0.2 g, 2.6 mmol, 1.1 eq.) was added and the reaction refluxed for 7 h. Potassium hydroxide (0.2 g, 3.6 mol, 1.5 eq.) dissolved in water (1 mL) was added to the reaction and heating continued for 1 h.

The solution was diluted with 1N sodium hydroxide (25 mL). The aqueous phase was extracted with dichloromethane (25 mL, 3X). The pH was adjusted to 4 with concentrated HCl and **506** precipitated. A 30 % yield was obtained. LCMS (APCI $^+$) 171 m+1/z. ^{1}H NMR (DMSO-d_6) δ 7.9 (d, IH, Ar), 7.1 (d, 1H, Ar), 2.7 (s, 3H, CH_3).

Step D:



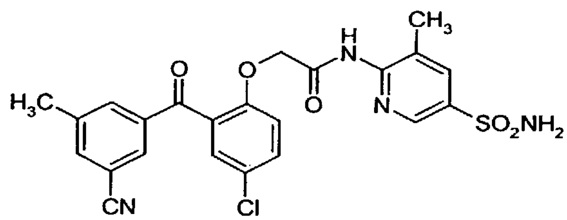
507

506 (0.115g, 0.67 mmol) was stirred in 1N HCl (5 mL) and chilled to 5 °C . Chlorine gas was passed through the mixture for 30 min. then the reaction was stirred for an additional 15 min. The product was extracted with dichloromethane (5 mL, 2X). The organic fractions were combined and chilled to 0 °C. Ammonia was dripped into the solution for 15 min. by condensing ammonia gas with a –78 °C cold finger. The reaction was allowed to warm to rt and stir overnight. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate (15 mL) and washed with $NaHCO_3$ solution (15 mL). The solution was dried with $MgSO_4$, filtered and the solvent removed in vacuo to give **507** in 40% yield suitable for further use. GCMS (CI $^+$) 218 m+1/z. ^{1}H NMR (DMSO-d_6) δ 8.6 (d, IH, Ar), 7.9 (d, 1H, Ar), 7.7 (bs, 2H, NH_2), 2.8 (s,3H, CH_3).

Step E:

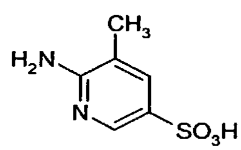
Reduction of the 5-nitro group of **507** (0.06 g, 0.27 mmol) was accomplished by catalytic reduction in ethanol (10 mL) with 10%Pd/C (0.011 g). The reaction was carried out overnight. The catalysis was removed by filtration and the amino compound was coupled with the acid chloride **589** generated by general procedure V, by the method outlined in general procedure VI to give **503** LCMS (ES $^+$) 499 m+1/z. ^{1}H NMR (DMSO-d_6) δ 9.6 (br s, 1H, NH), 8.0 (d, 1H, Ar), 7.94 (s, IH, Ar), 7.89 (s, 1H, Ar), 7.87 (s, 1H, Ar), 7.7 (d,1H, Ar), 7.6 (dd, 1H, Ar), 7.45 (d, 1H, Ar), 7.32 (bs, 2H, NH_2), 7.2 (d,1H, Ar), 4.8 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.33 (s, 3H, CH_3).

Example 207:



508

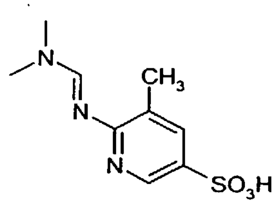
Step A:



509

3-Methyl-2-pyridinamine (1 mL, 1 mmol, Aldrich Chemical Co.) was combined with 20% fuming sulfuric acid (2 mL) at rt. The reaction was heated to 160 °C for 20 h. The reaction was allowed to cool to rt and ice, ~10 mL, was added. The product precipitated and was collected by filtration. A 50 % yield of **509** was obtained. LCMS (ES $^+$) 189 m+1/z. ^1H NMR (DMSO-d_6) δ 13(br s, 1H, SO_3H), 7.88(s, 3H, 1-Ar, 2H, NH_2), 7.87 (s, 1H, Ar), 2.14 (s,3H, CH_3).

Step B:

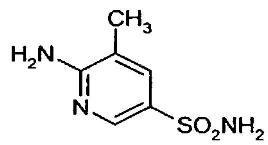


510

509 (0.9g, 4.8 mmol) was mixed with DMF (30 mL). Thionyl chloride (0.5 mL, 6.8 mmol, 1.4 eq.) was added and reaction stirred at rt. Solution was achieved briefly. A new precipitate formed. The reaction was stirred 30-40 min and filtered. The product was

washed with hexane and was suitable for further use. A 77% yield of **510** was obtained. LCMS (ES $^+$) 244 m+1/z. ^{1}H NMR (DMSO-d_6) δ 8.4 (s, 1H, formyl-H), 7.9 (s, 2H, Ar), 3.4 (s, 3H, CH_3), 3.3 (s, 3H, CH_3), 2.35 (s,3H, CH_3).

Step C:



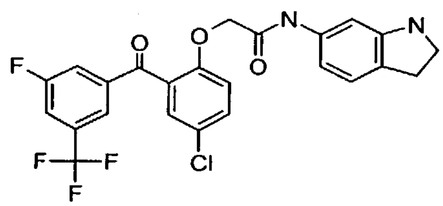
511

510 (1.0 g, 4.1 mmol) and PCl_5 (0.85 g, 4.1 mmol) were combined and heated in a 130 °C oil bath for 1.5 h. The resultant $POCl_3$ was removed under high vacuum. Concentrated ammonium hydroxide (25 mL) was carefully added at rt. The reaction was heated to reflux for 3 to 4 h and was then allowed to stand at rt for 60 h. The product was collected by filtration. A 45% yield of **511** was obtained. LCMS (ES $^+$) 188 m+1/z. ^{1}H NMR (DMSO-d_6) δ 8.12 (s, 1H, Ar), 7.5 (s, 1H, Ar), 7.0 (s, 2H, NH_2), 6.45 (s, 1H, Ar), 2.0 (s,3H, CH_3).

Step D:

511 (0.07g, 0.37 mmol) was mixed with THF (5 mL) and $(TMS)_2BSA$ (0.090 mL, 2 eq.). The reaction was refluxed for 45 min. The solution was cooled to rt and the acid chloride of acid (1eq.) 589, prepared by general procedure V, was added. The reaction was stirred for 2 h at rt. The solvent was removed in vacuo. Partial purification of the product was accomplished by chromatography on a 4 X 6 cm column of silica gel eluted with chloroform/ methanol (96:4) followed by chromatography on a 4 X 6 cm column of silica gel eluted with chloroform/ methanol (95:5). Final purification was accomplished by HPLC on a Waters Symmetry C18 column, 1.9 X 15 cm, eluted with MeOH/H_2O (3:2) at 8 mL/min. A 10% yield of 508 was obtained. LCMS (APCI $^+$) 499 m+1/z. ^{1}H NMR (DMSO-d_6) δ 10.2 (br s, 1H, NH), 8.56(s, 1H, Ar), 7.98 (s, 1H, Ar), 7.91 (s, 1H, Ar), 7.87 (s, 2H, Ar), 7.60 (dd,1H, Ar), 7.47 (s, 2H, NH_2), 7.44 (s, 1H, NH_2), 7.12 (d,1H, Ar), 4.8 (s, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.10 (s, 3H, CH_3).

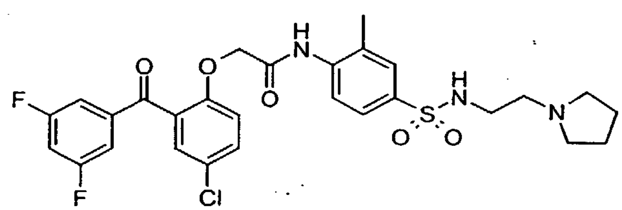
Example 208:



512

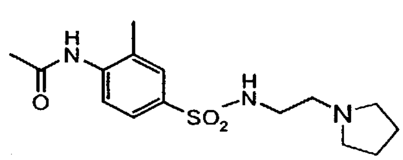
Carboxylic acid **71** (0.258 g, 0.68 mmol), oxalyl chloride (0.8 mL of 2.0 M solution in dichloromethane, 0.92 mmol), DMF (8 drops), and dichloromethane (5 mL), were used to prepare the acid chloride according to general procedure V. The acid chloride was then dissolved in acetone and added dropwise to 6-aminoindoline dihydrochloride (Aldrich, 0.140 g, 0.68 mmol), acetone (10 mL), sodium bicarbonate (0.501 g, 6 mmol), and water (1 mL) as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered, washed with water and diethyl ether, then air dried. The solids were then purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **512** (0.06 g, 18%). ^1H NMR (DMSO-d_6, 300 MHz) δ 2.92 (t, 2H), 3.94 (t, 2H), 4.93 (m, 3H), 6.21 (dd, 1H), 6.84 (d, 1H), 7.19 (d, 1H), 7.32 (m, 1H), 7.51 (d, 1H), 7.58 (dd, 1H), 8 (m, 3H); LC-MS (ES$^+$) *m/z* 493 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 491 (M-H)$^-$.

Example 209:



513

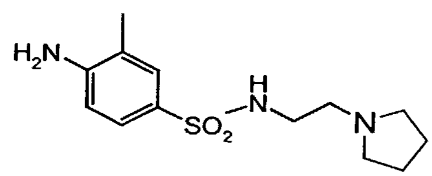
Step A:



514

A mixture of **464** (1.10 g, 4.4 mmol), 1-(2-aminoethyl)pyrrolidine (0.84 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in methylene chloride (50 mL) was stirred rt for 6 d. The reaction mixture was then diluted with 50 mL of CH_2Cl_2 and extracted with two 50-mL portions of water. The organic layer was dried over $MgSO_4$ and filtered to give 1.021 g of a brown oil. Purification by flash chromatography (elution with 3-5% $MeOH/CH_2Cl_2$) gave **514** as a yellow oil (0.776 g, 54%): MS (ES+) *m/z* 326 (M+H); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.19-8.17 (m, 1 H), 7.70-7.68 (m, 2 H), 7.19 (br s, 1 H), 2.98 (t, 2 H), 2.52 (t, 2 H), 2.37-2.34 (m, 4 H), 2.32 (s, 3 H), 2.25 (s, 3 H), 1.73-17.0 (m, 4 H).

Step B:



515

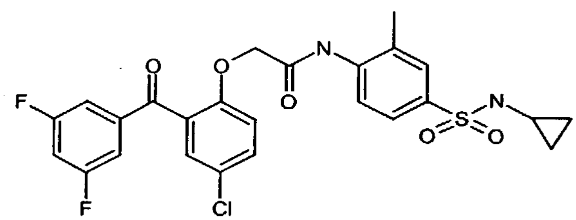
A mixture of **514** (0.765 g, 2.35 mmol) and 1.5 M HCl (5 mL) in 20 mL of ethanol was heated to 80 °C for 18 h. The reaction mixture was then poured into 50 mL of saturated $NaHCO_3$ (aq) and extracted with two 30-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **515** (0.564 g, 81%): MS (ES+) *m/z* 284 (M+H); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54-7.50 (m, 2 H), 6.68 (d, 1 H), 4.07 (br s, 2 H), 2.98-2.95 (m, 2 H), 2.54-2.52 (m, 2 H), 2.39-2.32 (m, 4 H), 2.18 (s, 3 H), 1.75-1.68 (m, 4 H).

Step C:

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **515** (0.07 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to afford **513** as an off-white solid (0.015 g, 8.7%). ^1H NMR (DMSO-

d_6, 300 MHz) δ 1.65 (m, 4H), 2.2 (s, 3H), 2.85 (t, 2H), 3.35 (m, 6H), 4.83 (s, 2H), 7.22 (d, 1H), 7.43-7.72 (m, 8H), 9.48 (s, 1H); MS (ES^+) m/z 592 $(M+H)^+$.

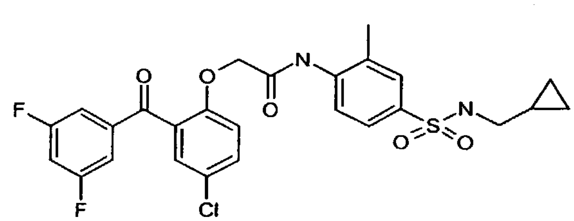
Example 210:



516

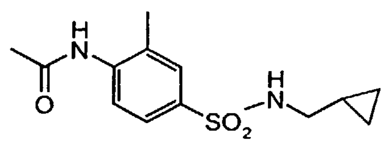
Acid **49** was converted to the acid chloride using the general procedure V. Aniline **315** (0.066 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solid was dissolved in CH_2Cl_2 then chromatographed by TLC prep plate eluded with 9:1 CH_2Cl_2:MeOH to afford **516** as an off-white solid (0.074 g, 48%). ^1H NMR (DMSO-d_6, 400 MHz) δ 0.4 (m, 2H), 0.42 (m, 2H), 2 (m, 1H), 2.2 (s, 3H), 4.8 (s, 2H), 7.18 (d, 1H), 7.38 (m, 2H), 7.41 (d, 1H), 7.46-7.61 (m, 4H), 7.69 (d, 1H), 7.76 (d, 1H), 9.38 (s, 1H); MS (ES^+) m/z 535 $(M+H)^+$, MS (ES^-) m/z 533 $(M-H)^-$.

Example 211:



517

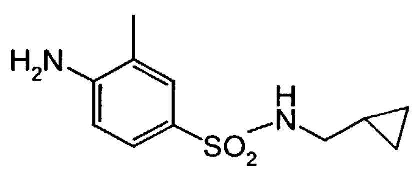
Step A:



518

A mixture of **464** (1.10 g, 4.4 mmol), cyclopropanemethylamine (Aldrich, 0.57 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at rt for 7 d. The reaction mixture was then filtered, washed with 50 mL of CH_2Cl_2 and 50 mL of water. The organic layer was washed with an additional 50 mL of water, brine, dried over $MgSO_4$, filtered and concentrated. Crystallization of the crude material from MeOH provided **518** (0.348 g, 28%): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.39 (s, 1 H), 7.72 (d, 1 H), 7.58-7.52 (m, 3 H), 2.59 (t, 2 H), 2.25 (s, 3 H), 2.07 (s, 3 H), 0.80-0.72 (m, 1 H), 0.34-0.29 (m, 2 H), 0.06-0.03 (m, 2 H).

Step B:



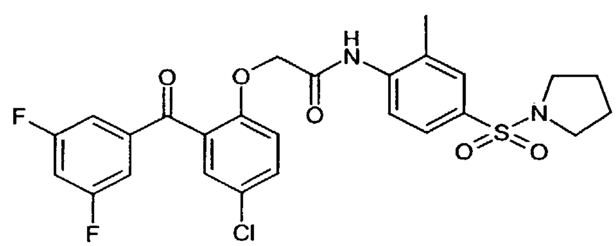
519

A mixture of **518** (0.310 g, 1.1 mmol) and 1.5 M HCl (2.5 mL) in 12 mL of ethanol was heated to 80 °C for 18 h. The reaction mixture was then poured into 50 mL of saturated $NaHCO_3$ (aq) and extracted with two 30-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **519**, which was used without further purification (0.284 g): MS (ES+) *m/z* 241 (M+H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54-7.51 (m, 2 H), 6.68 (d, 1 H), 4.41 (t, 1 H), 4.06 (br s, 2 H), 2.78 (t, 2 H), 2.18 (s, 3 H), 0.92-0.83 (m, 1 H), 0.48-0.43 (m, 2 H), 0.11-0.07 (m, 2 H).

Step C:

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **519** (0.07 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to afford **517** as an off-white solid (0.129 g, 81%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.1 (m, 2H), 0.36 (m, 2H), 0.82 (m, 1H), 2.2 (s, 3H), 2.64 (t, 2H), 4.86 (s, 2H), 7.25 (d, 1H), 7.46-7.74 (m, 9H), 9.44 (s, 1H); MS (ES$^+$) *m/z* 549 (M+H)$^+$, MS (ES$^-$) *m/z* 547 (M-H)$^-$.

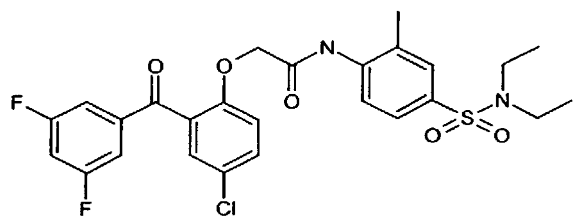
Example 212:



520

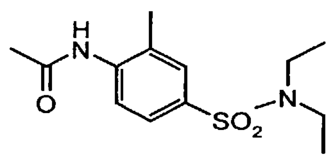
Acid **49** was converted to the acid chloride using the general procedure V. Aniline **318** (0.07 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to afford **520** as an off-white solid (0.126 g, 79%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.66 (m, 4H), 2.26 (s, 3H), 3.35 (m, 4H), 4.87 (s, 2H), 7.25 (d, 1H), 7.47-7.7 (m, 7H), 7.82 (d, 1H), 9.43 (s, 1H); MS (ES$^+$) *m/z* 549 (M+H)$^+$, MS (ES$^-$) *m/z* 547 (M-H)$^-$.

Example 213:



521

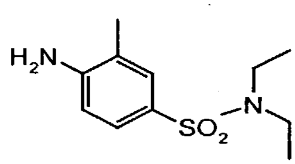
Step A:



522

A mixture of **464** (1.10 g, 4.4 mmol), diethylamine (0.68 mL, 6.6 mmol), and pyridine (0.39 mL, 4.8 mmol) in 50 mL of methylene chloride was stirred at rt for 5 d. The reaction mixture was then diluted with 100 mL of CH_2Cl_2 and washed with two 50-mL portions of water. The organic layer was washed with brine, dried over $MgSO_4$, and filtered to give 1.2 g of an orange oil. Crystallization from EtOAc/hexane gave **522** as orange crystals (0.446 g, 36%): MS (ES+) *m/z* 285 (M+H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, 1 H), 7.61-7.58 (m, 2 H), 3.21 (q, 4 H), 2.29 (s, 3 H), 2.24 (s, 3 H), 1.13 (t, 6 H).

Step B:



523

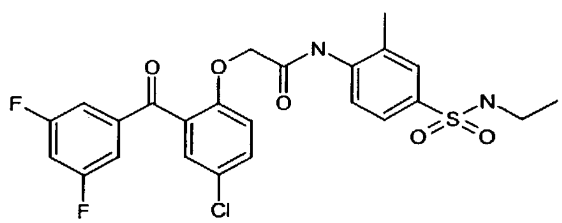
A mixture of **522** (0.341 g, 1.2 mmol) and 1.5 M HCl (2.5 mL) in 12 mL of ethanol was heated to 80 °C for 18 h. The reaction mixture was then poured into 50 mL of saturated $NaHCO_3$ (aq) and extracted with two 30-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **523** as a yellow

solid (0.285 g, 98%): MS (ES+) *m/z* 243 (M+H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48-7.45 (m, 2 H), 6.66 (d, 1 H), 4.02 (br s, 2 H), 3.19 (q, 4 H), 2.18 (s, 3 H), 1.12 (t, 6 H).

Step C:

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **523** (0.07 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were washed with ether to afford **521** as an off-white solid (0.117 g, 73%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.06 (t, 6H), 2.24 (s, 3H), 3.16 (m, 4H), 4.86 (s, 2H), 7.25 (d, 1H), 7.47-7.70 (m, 7H), 7.77 (d, 1H), 9.43 (s, 1H); MS (ES$^+$) *m/z* 551 (M+H)$^+$, MS (ES$^-$) *m/z* 549 (M-H)$^-$.

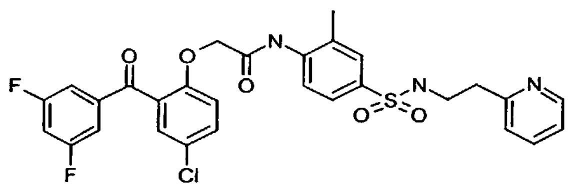
Example 214:



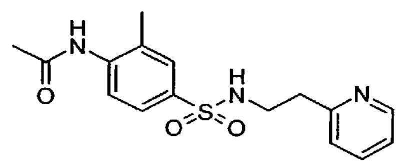
524

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **312** (0.062 g, 0.29 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.1 g, 0.29 mmol) were used as in general procedure VI. Water (25 mL) was added to the reaction mixture and the resulting suspension was filtered. The solid was washed with ether to afford **524** as an off-white solid (0.109 g, 70%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.99 (t, 3H), 2.23 (s, 3H), 2.77 (m, 2H), 4.86 (s, 2H), 7.25 (d, 1H), 7.46-7.75 (m, 9H), 9.45 (s, 1H); MS (ES$^+$) *m/z* 523 (M+H)$^+$, MS (ES$^-$) *m/z* 521 (M-H)$^-$.

Example 215:



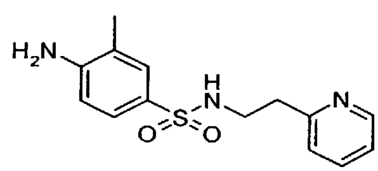
525



526

Step A:

Sulfonyl chloride **464** (0.27 g, 1.09 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and 2-(2-aminoethyl)pyridine (Aldrich, 0.28 g, 2.3 mmol). The mixture was allowed to stir for 2 d. Water was added and the mixture was extracted with dichloromethane, concentrated, and purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **526** (0.70 g, 51%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.05 (s, 3H), 2.22 (s, 3H), 2.77 (t, 2H), 3.03 (t, 2H), 7.13 (dd, 2H), 7.48-7.71 (m, 5H), 8.38 (dd, 1H), 9.37 (s, 1H).



527

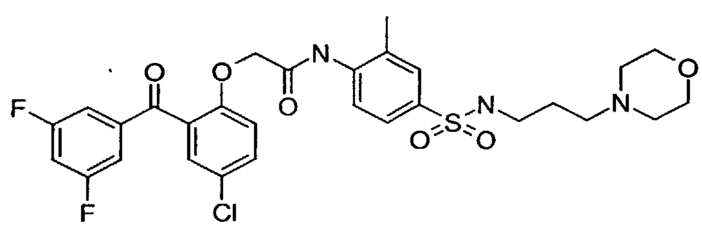
Step B:

Sulfonamide **526** (0.7 g, 2.09 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **527** (0.11 g, 18%). The crude product was used without further purification.

Step C:

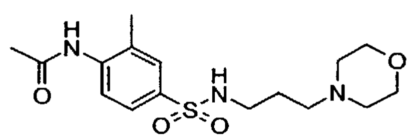
Acid **49** was converted to the acid chloride using the general procedure V. Aniline **527** (0.05 g, 0.17 mmol), the acid chloride (0.19 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) were used as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **525** (0.03 g, 33%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.18 (s, 3H), 2.81 (t, 2H), 3.08 (m, 2H), 4.83 (s, 2H), 7.16-7.23 (m, 3H), 7.43-7.7 (m, 10H), 8.42 (m, 1H), 9.41 (s, 1H); MS (ES^+) *m/z* 600 $(M+H)^+$, MS (ES^-) *m/z* 598 $(M-H)^-$.

Example 216:



528

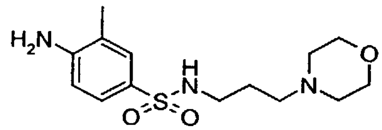
Step A:



529

Sulfonyl chloride **464** (0.27 g, 1.09 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and aminopropylmorpholine (Aldrich, 0.33 g, 2.3 mmol). The mixture was allowed to stir for 2 d, followed by the addition of water and extraction with dichloromethane. The organic layer was concentrated, and the product purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **529** (0.7 g, 49%). ^1H NMR (DMSO-d_6, 400 MHz) δ 1.44 (m, 2H), 2.05 (s, 3H), 2.12 (m, 4H), 2.23 (s, 2H), 2.7 (m, 2H), 3.45 (m, 4H), 7.41 (t, 1H), 7.5 (dd, 1H), 7.55 (d, 1H), 7.71 (d, 1H), 9.38 (s, 1H).

Step B:



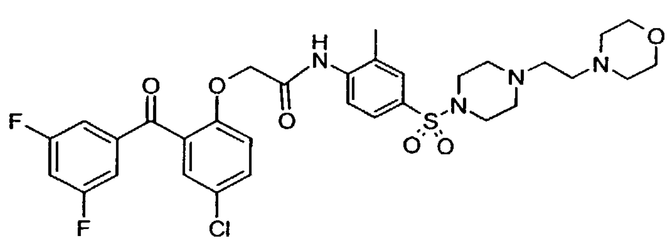
530

Sulfonamide **529** (0.7 g, 1.96 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **530** (0.15 g, 24%). The crude product was used without further purification.

Step C:

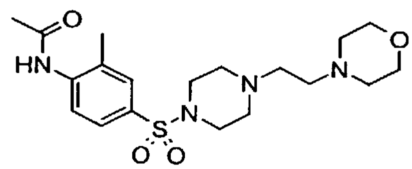
Acid **49** was converted to the acid chloride using the general procedure V. Aniline **530** (0.05 g, 0.16 mmol), the acid chloride (0.19 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) were used as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The product was purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **528** (0.01 g, 6%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.8 (m, 1H), 1.18 (s, 1H), 1.43 (m, 2H), 2.15 (m, 7H), 2.7 (m, 2H), 3.44 (m, 4H), 4.78 (s, 2H), 7.18 (d, 1H), 7.39-7.67 (m, 9H), 9.38 (s, 1H); LC-MS (ES$^+$) *m/z* 623 (M+H)$^+$, MS (ES$^-$) *m/z* 621 (M-H)$^-$.

Example 217:



531

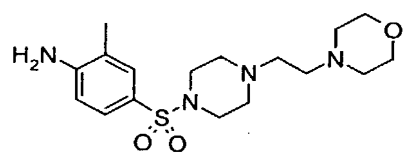
Step A:



532

Sulfonyl chloride **464** (0.27 g, 1.09 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and 1-(2-morpholinoethyl)piperazine (EMKA, 0.46 g, 2.3 mmol). The mixture was allowed to stir for 2 , followed by the addition of and extraction with dichloromethane. The organic layer was concentrated, and the product was purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **532** (0.3 g, 19%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.07 (s, 3H), 2.27 (m, 9H), 2.38 (m, 2H), 2.45 (m, 4H), 2.85 (m, 2H), 3.3 (m, 2H), 3.5 (m, 4H), 7.46 (m, 2H), 7.82 (d, 1H), 9.4 (s, 1H).

Step B:



533

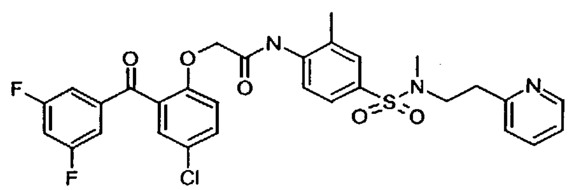
Sulfonamide **532** (0.3 g, 0.73 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **533** (0.08 g, 30%). The crude product was used without further purification.

Step C:

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **533** (0.05 g, 0.14 mmol), the acid chloride (0.19 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) were used as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The product was purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **531** (0.01 g, 7%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3H), 2.38-2.54 (m, 12H), 2.97 (bs,

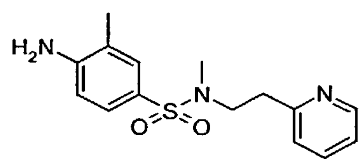
4H), 3.63 (m, 4H), 4.69 (s, 2H), 7-7.1 (m, 2H), 7.29-7.35 (m, 3H), 7.51-7.57 (m, 3H), 8.1 (d, 1H), 8.66 (s, 1H).

Example 218:



534

Step A:



535

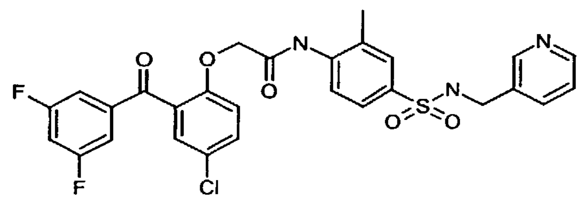
Sulfonyl chloride **464** (3 mmol), pyridine (5 mL), and 2-(2-methylaminoethyl)pyridine (Aldrich, 0.41 g, 3.01 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 d. Water was added and the mixture was extracted with dichloromethane, and the organic layer was concentrated in vacuo. The resulting products were then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solution was concentrated in vacuo and the product was purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **535** (0.28 g, 30%).

Step B:

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **535** (0.05 g, 0.16 mmol), the acid chloride (0.15 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) were used as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The solid was then purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **534** (0.04 g, 40%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.21 (s, 3H), 2.67 (s, 3H), 2.93 (m, 2H),

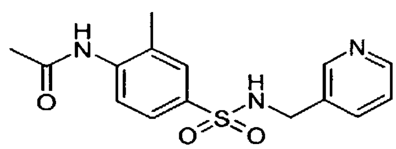
4.08 (m, 2H), 4.83 (s, 2H), 7.18-7.27 (m, 3H), 7.43-7.77 (m, 9H), 8.46 (m, 1H), 9.41 (s, 1H); LC-MS (ES^+) *m/z* 614 $(M+H)^+$, LC-MS (ES^-) *m/z* 612 $(M-H)^-$.

Example 219:



536

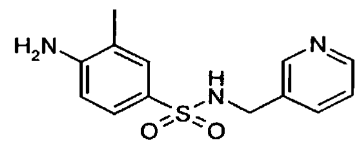
Step A:



537

Sulfonyl chloride **464** (3 mmol), pyridine (5 mL), and 3-picolylamine (Aldrich, 0.25 g, 2.3 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 d followed by the addition of water. The reaction mixture was extracted with dichloromethane, and the organic layer was separated and concentrated in vacuo. The product was purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **537** (0.9 g, 67%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.06 (s, 3H), 2.22 (s, 3H), 3.96 (d, 2H), 7.24 (dd, 1H), 7.54 (m, 3H), 7.71 (d, 1H), 8.06 (t, 1H), 8.36 (d, 2H), 9.37 (s, 1H).

Step B:



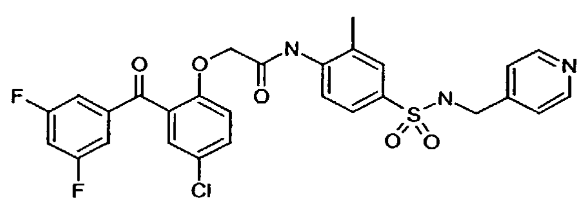
538

Sulfonamide **537** (0.9 g, 2.81 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **538** (0.25 g, 32%). The crude product was used without further purification.

Step C:

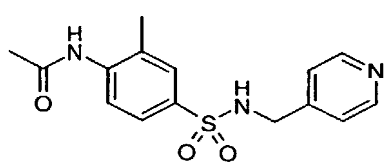
Acid **49** was converted to the acid chloride using the general procedure V. Aniline **538** (0.05 g, 0.18 mmol), the acid chloride (0.15 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The product was purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **536** (0.03 g, 27%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.18 (s, 3H), 4 (d, 2H), 4.83 (s, 2H), 7.22 (d, 1H), 7.28 (dd, 1H), 7.45 (m, 2H), 7.51 (d, 1H), 7.57-7.72 (m, 6H), 8.13 (t, 1H), 8.41 (m, 2H), 9.42 (s, 1H); LC-MS (ES$^+$) m/z 586 $(M+H)^+$, LC-MS (ES$^-$) m/z 584 $(M-H)^-$.

Example 220:



539

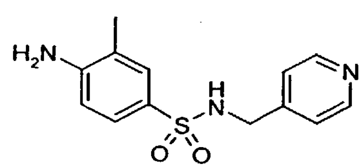
Step A:



540

Sulfonyl chloride **464** (1.1 mmol), pyridine (5 mL), and 4-picolylamine (Aldrich, 0.25 g, 2.3 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 d followed by the addition of water. The mixture was extracted with dichloromethane, the organic layer was separated and concentrated in vacuo. The product was purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **540** (0.5 g, 37%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.06 (s, 3H), 2.21 (s, 3H), 3.95 (d, 2H), 7.21 (d, 2H), 7.52 (m, 2H), 7.71 (m, 1H), 8.14 (t, 1H), 8.41 (dd, 2H), 9.38 (s, 1H).

Step B:

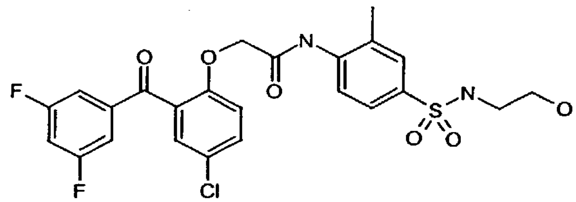


Sulfonamide **540** (0.5 g, 1.56 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **541** (0.12 g, 28%). The crude product was used without further purification.

Step C:

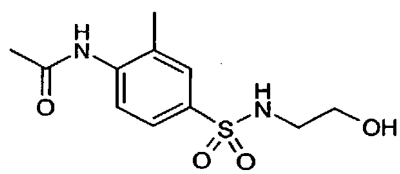
Acid **49** was converted to the acid chloride using the general procedure V. Aniline **541** (0.05 g, 0.18 mmol), the acid chloride (0.15 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The product was purified by flash chromatography and TLC prep plate using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **539** (0.02 g, 19%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.18 (s, 3H), 4.01 (m, 2H), 4.83 (s, 2H), 7.21-7.26 (m, 3H), 7.43-7.72 (m, 8H), 8.2 (t, 1H), 8.45 (m, 2H), 9.42 (s, 1H); LC-MS (ES$^+$) m/z 586 $(M+H)^+$, LC-MS (ES$^-$) m/z 584 $(M-H)^-$.

<u>**Example 221:**</u>



542

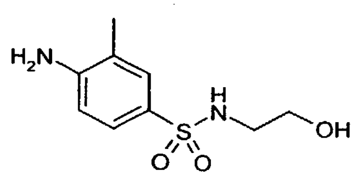
Step A:



543

Sulfonyl chloride **464** (1.1 mmol), pyridine (5 mL), and ethanolamine (Aldrich, 0.14 g, 2.3 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 d followed by the addition of water. The mixture was extracted with dichloromethane, the organic layer was separated and concentrated in vacuo. The product was purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **543** (0.46 g, 37%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.05 (s, 3H), 2.23 (s, 3H), 2.7 (m, 2H), 3.29 (m, 2H), 4.62 (t, 1H), 7.41 (t, 1H), 7.51 (dd, 1H), 7.56 (d, 1H), 7.7 (d, 1H), 9.38 (s, 1H).

Step B;



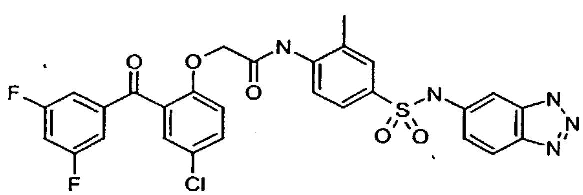
544

Sulfonamide **549** (0.46 g, 1.68 mmol), 1.5 N HCl (10 mL), and ethanol (10 mL) were used according to general procedure XVII to afford **544** (0.12 g, 31%). The crude product was used without further purification.

Step C:

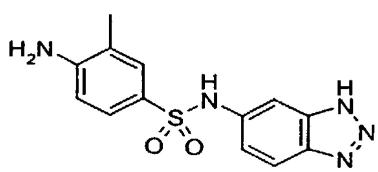
Acid **49** was converted to the acid chloride using the general procedure V. Aniline **544** (0.05 g, 0.22 mmol), the acid chloride (0.15 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The product was purified by flash chromatography and TLC prep plate using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **542** (0.02 g, 17%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.2 (s, 3H), 2.75 (q, 2H), 3.34 (m, 2H), 4.66 (t, 1H), 4.83 (s, 2H), 7.22 (d, 1H), 7.42-7.72 (m, 9H), 9.42 (s, 1H); LC-MS (ES$^+$) *m/z* 539 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 537 (M-H)$^-$.

Example 222:



545

Step A:



546

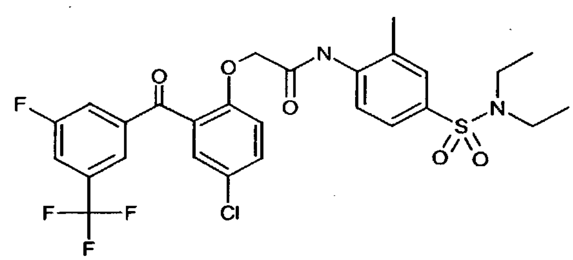
Sulfonyl chloride **464** (3 mmol), pyridine (5 mL), and 5-aminobenzotriazole (Lancaster, 0.41 g, 3.06 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 days. Water was added and the mixture was extracted with dichloromethane, the organics were separated, concentrated in vacuo. The resulting products were then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated, with stirring, to 60 °C overnight. The resulting solution was concentrated in vacuo and purified by flash

chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **546** (0.45 g, 48%). The crude product was used without further purification.

Step B:

Acid **49** was converted to the acid chloride using the general procedure V. Aniline **546** (0.05 g, 0.16 mmol), the acid chloride (0.15 mmol), acetone (5 mL), sodium bicarbonate (0.3 g, 3.57 mmol), and water (4 drops) as in general procedure VI. Ice (5 mL) was added to the reaction mixture and the resulting suspension was filtered. The solids were then purified by flash chromatography and TLC prep plate using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **545** (0.01 g, 10%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.13 (s, 3H), 4.78 (s, 2H), 7.16 (m, 2H), 7.39-7.85 (m, 11H), 9.34 (s, 1H) 10.5 (bs, 1H); LC-MS (ES$^+$) *m/z* 586 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 584 (M-H)$^-$.

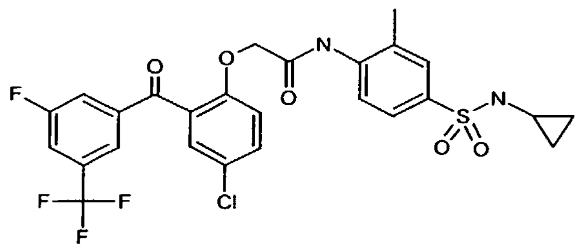
__Example 223:__



547

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **523** (0.1 g, 0.41 mmol), the acid chloride (0.16 g, 0.4 mmol), acetone (4 mL), and sodium bicarbonate (0.22 g, 2.6 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **547** (0.085 g, 34%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.02 (t, 6H), 2.18 (s, 3H), 3.12 (m, 4H), 4.81 (s, 2H), 7.22 (d, 1H), 7.54-7.71 (m, 5H), 7.87 (d, 2H), 7.98 (d, 1H), 9.38 (s, 1H); LC-MS (ES$^+$) *m/z* 601 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 599 (M-H)$^-$.

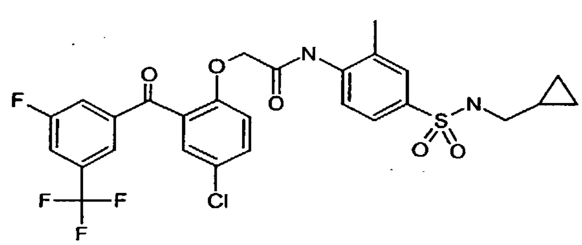
__Example 224:__



548

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **315** (0.1 g, 0.44 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.4 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography and TLC prep plate using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **548** (0.074 g, 29%). ^1H NMR (DMSO-d_6, 300 MHz) δ 0.3-0.5 (m, 4H), 2.04 (m, 1H), 2.18 (s, 3H), 4.81 (s, 2H), 7.24 (d, 1H), 7.54-7.88 (m, 8H), 8 (d, 1H), 9.41 (s, 1H); LC-MS (ES^+) *m/z* 585 $(M+H)^+$, LC-MS (ES^-) *m/z* 583 $(M-H)^-$.

__Example 225:__

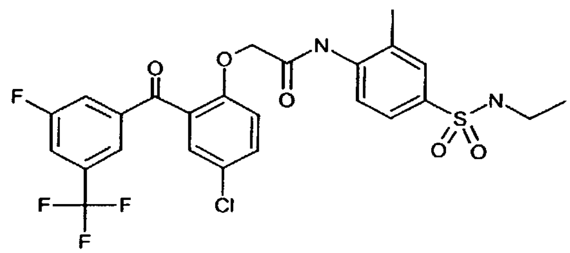


549

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **518** (0.1 g, 0.42 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.4 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **549** (0.095 g, 38%). ^1H NMR (DMSO-d_6, 300 MHz) δ 0.05 (m, 2H), 0.33 (m, 2H), 0.77 (m, 1H), 2.16 (s, 3H), 2.6

(d, 2H), 4.8 (s, 2H), 7.22 (d, 1H), 7.54-7.67 (m, 6H), 7.86 (d, 2H), 8 (d, 1H), 9.4 (s, 1H); LC-MS (ES^+) *m/z* 599 $(M+H)^+$, LC-MS (ES^-) *m/z* 597 $(M-H)^-$.

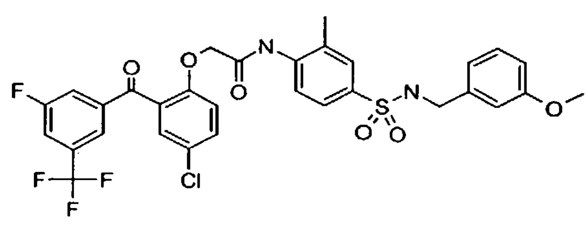
Example 225:



550

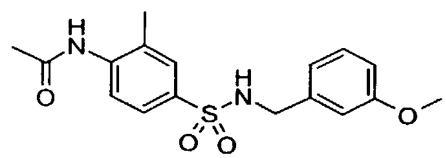
Acid **71** was converted to the acid chloride using the general procedure V. Aniline **312** (0.1 g, 0.42 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.4 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **550** (0.125 g, 47%). ^1H NMR (DMSO-d_6, 300 MHz) δ 0.94 (t, 3H), 2.17 (s, 3H), 2.72 (m, 2H), 4.81 (s, 2H), 7.22 (d, 1H), 7.43 (t, 1H), 7.53-7.68 (m, 5H), 7.87 (d, 2H), 8 (d, 1H), 9.4 (s, 1H); LC-MS (ES^+) *m/z* 573 $(M+H)^+$, LC-MS (ES^-) *m/z* 571 $(M-H)^-$.

Example 226:



551

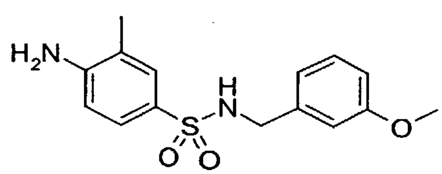
Step A:



552

Sulfonyl chloride **464** (3 mmol), pyridine (5 mL), and 3-methoxybenzylamine (Aldrich, 0.41 g, 3.01 mmol) were used as in general procedure XVI. The mixture was allowed to stir for 2 d. The resulting mixture was concentrated in vacuo. Water was added and the mixture was filtered to afford **552** (0.24 g, 69%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.06 (s, 3H), 2.21 (s, 3H), 3.63 (s, 3H), 3.89 (d, 2H), 6.73 (m, 3H), 7.13 (t, 1H), 7.53 (m, 2H), 7.7 (d, 1H), 7.96 (t, 1H), 9.36 (s, 1H); LC-MS (ES$^+$) *m/z* 349 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 347 (M-H)$^-$.

Step B:



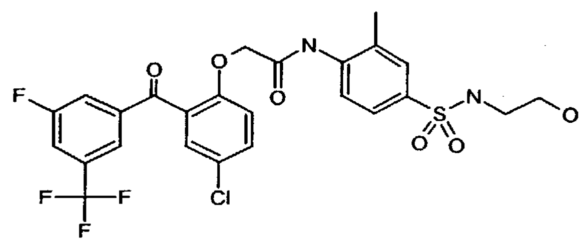
553

The sulfonamide **552** was dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL). The resulting mixture was heated to 60 °C overnight. The resulting solution was concentrated in vacuo to afford **553.** The product was used without further purification.

Step C:

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **553** (0.1 g, 0.33 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **551** (0.212 g, 98%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.14 (s, 3H), 3.66 (s, 3H), 3.92 (d, 2H), 4.81 (s, 2H), 6.77 (t, 3H), 7.13-7.24 (m, 2H), 7.55 (m, 3H), 7.66 (dd, 2H), 7.87 (m, 2H), 8.02 (t, 2H), 9.4 (s, 1H); LC-MS (ES$^+$) *m/z* 665 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 663 (M-H)$^-$.

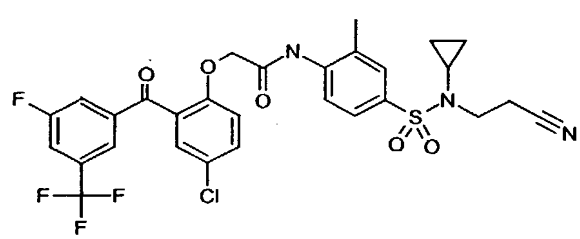
Example 227:



554

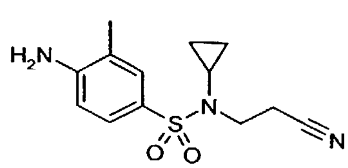
Acid **71** was converted to the acid chloride using the general procedure V. Aniline **544** (0.1 g, 0.43 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **554** (0.073 g, 29%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.17 (s, 3H), 2.74 (m, 2H), 3.35 (m, 2H), 4.65 (t, 1H), 4.81 (s, 2H), 7.22 (d, 1H), 7.45-7.68 (m, 6H), 7.87 (d, 2H), 8 (d, 1H), 9.41 (s, 1H); LC-MS (ES$^+$) *m/z* 589 $(M+H)^+$, LC-MS (ES$^-$) *m/z* 587 $(M-H)^-$.

Example 228:



555

Step A:



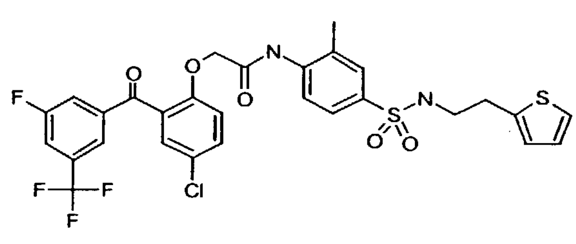
556

Sulfonyl chloride **464** (3 mmol), pyridine (5 mL), and 3-(cyclopropylamino)propionitrile (Trans World Chemical, 0.33 g, 3 mmol) were used as in general procedure XXVI. The mixture was allowed to stir for 2 d, followed by the addition of water and extraction with dichloromethane. The organic layer was separated and concentrated in vacuo. The resulting products were then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solution was concentrated in vacuo and the product purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **556** (0.22 g, 26%).

Step B:

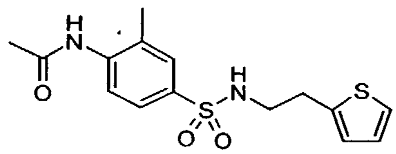
Acid **71** was converted to the acid chloride using the general procedure V. Aniline **556** (0.1 g, 0.36 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solution was concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **556** (0.113 g, 49%). ^1H NMR (DMSO-d_6, 300 MHz) δ 0.63-0.82 (m, 4H), 2 (m, 1H), 2.21 (s, 3H), 2.78 (t, 2H), 3.36 (m, 2H), 4.82 (s, 2H), 7.22 (d, 1H), 7.54 (d, 1H), 7.63 (m, 3H), 7.79 (d, 1H), 7.87 (d, 2H), 8 (d, 1H), 9.42 (s, 1H); LC-MS (ES$^+$) *m/z* 638 $(M+H)^+$, LC-MS (ES$^-$) *m/z* 638 $(M-H)^-$.

Example 229:



557

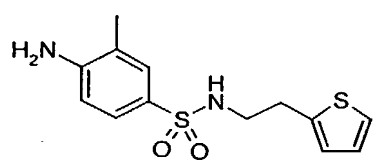
Step A:



558

Sulfonyl chloride **464** (3 mmol), pyridine (5 mL), and thiophene-2-ethylamine (Aldrich, 0.41 g, 3.01 mmol) were used as in general procedure XVI. The mixture was allowed to stir at rt for 2 d, followed by concentration in vacuo. Water was added to the resulting residue and the mixture was filtered to afford the protected sulfonamide **558** (0.12 g, 35%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.05 (s, 3H), 2.23 (s, 3H), 2.81-2.93 (m, 4H), 6.79 (d, 1H), 6.87 (dd, 1H), 7.26 (dd, 1H), 7.51 (dd, 1H), 7.55 (s, 1H), 7.61 (t, 1H), 7.71 (d, 1H), 9.37 (s, 1H); LC-MS (ES$^+$) *m/z* 339 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 337 (M-H)$^-$.

Step B:



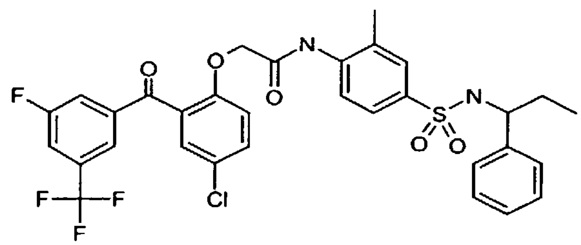
559

Sulfonamide **558** was dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solutions were concentrated in vacuo to afford **559**. The resulting product was used without further purification.

Step C:

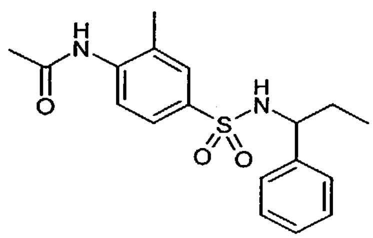
Acid **71** was converted to the acid chloride using the general procedure V. Aniline **559** (0.1 g, 0.34 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **557** (0.206 g, 93%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.16 (s, 3H), 2.87-2.95 (m, 4H), 4.8 (s, 2H), 6.83 (d, 1H), 6.91 (t, 1H), 7.22 (d, 1H), 7.3 (d, 1H), 7.54-7.68 (m, 6H), 7.87 (d, 2H), 8 (d, 1H), 9.4 (s, 1H); LC-MS (ES$^+$) *m/z* 654 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 653 (M-H)$^-$.

Example 230:



560

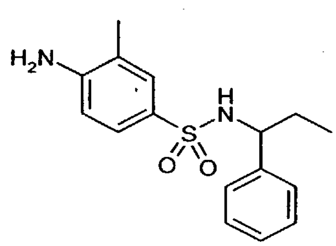
Step A:



561

Sulfonyl chloride **464** (3 mmol), pyridine (5 mL), and DL-1-phenylpropylamine (Norse, 0.41 g, 3.01 mmol) were used as in general procedure XXVI. The mixture was allowed to stir at rt for 2 d, followed by concentration in vacuo. Water was added to the resulting residue and the mixture was filtered to afford the protected sulfonamide **561** (0.19 g, 55%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.61 (t, 3H), 1.5 (m, 2H), 2.03 (s, 3H), 2.08 (s, 3H), 4.03 (m, 1H), 7.03-7.12 (m, 5H), 7.26 (d, 1H), 7.35 (dd, 1H), 7.56 (d, 1H), 8 (d, 1H), 9.24 (s, 1H); LC-MS (ES$^+$) *m/z* 347 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 345 (M-H)$^-$.

Step B:



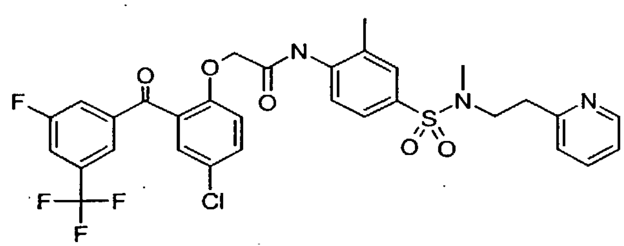
562

Sulfonamide **561** was dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solution was concentrated in vacuo to afford **562**. The resulting product was used without further purification.

Step C:

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **562** (0.1 g, 0.33 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solution was concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **560** (0.185 g, 85%). ^1H NMR (DMSO-d_6, 300 MHz) δ 0.63 (t, 3H), 1.55 (m, 2H), 2 (s, 3H), 4.06 (m, 1H), 4.85 (s, 2H), 7.04-7.15 (m, 5H), 7.22 (d, 1H), 7.3 (s, 1H), 7.39 (dd, 1H), 7.53 (m, 2H), 7.66 (dd, 1H), 7.87 (d, 2H), 7.99-8.07 (m, 2H), 9.29 (s, 1H); LC-MS (ES$^+$) *m/z* 663 $(M+H)^+$, LC-MS (ES$^-$) *m/z* 661 $(M-H)^-$.

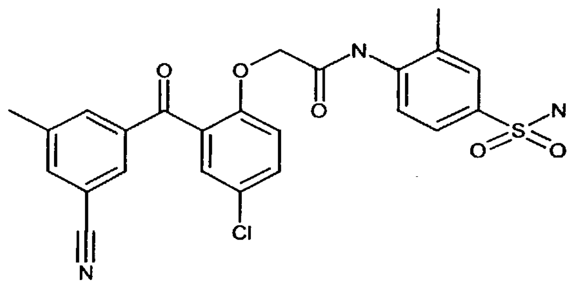
<u>Example 231:</u>



563

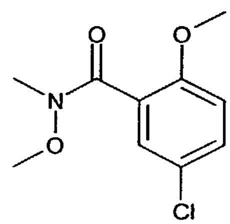
Acid **71** was converted to the acid chloride using the general procedure V. Aniline **535** (0.1 g, 0.33 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solution was concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **563** (0.193 g, 89%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.21 (s, 3H), 2.67 (s, 3H), 2.92 (t, 2H), 4.09 (m, 2H), 4.83 (s, 2H), 7.18-7.27 (m, 3H), 7.42-7.78 (m, 9H), 8.46 (m, 1H), 9.41 (s, 1H); LC-MS (ES$^+$) *m/z* 664 $(M+H)^+$, LC-MS (ES$^-$) *m/z* 662 $(M-H)^-$.

Example 232:



564

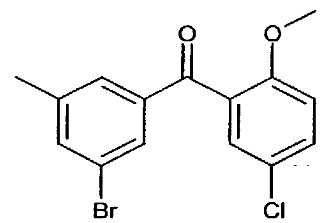
Step A:



565

5-Chloro-2-methoxybenzoic acid (Aldrich, 17.1 g, 91 mmol), oxalyl chloride (50 mL of 2.0 M solution in dichloromethane, 100 mmol), DMF (1.2 mL), and dichloromethane (100 mL), were used to prepare the acid chloride according to general procedure V. The mixture was concentrated after 2 h, dissolved in chloroform (50 mL), and added dropwise to a solution of N,O-dimethylhydroxylamine (Aldrich, 13.34 g, 140 mmol), chloroform (200 mL), and triethylamine (19.06 mL, 140 mmol) at 0 ^{0}C as in general procedure VII. After 1 h, water was added to the reaction mixture and the organic layer was separated. The aqueous was further extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **565** (18.69 g, 96%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.2 (bs, 3H), 3.45 (bs, 3H), 3.77 (s, 3H), 7.1 (d, 1H), 7.3 (d, 1H), 7.42 (m, 1H).

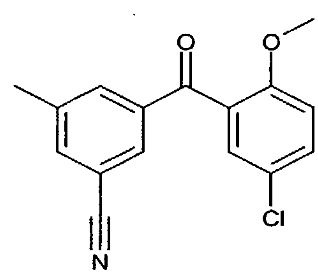
Step B:



566

Into a oven dried round-bottom flask equipped with a stir bar, nitrogen on demand, and an addition funnel, were added 3,5-dibromotoluene (Avocado, 20.85 g, 83.4 mmol), and methyl t-butyl ether (500 mL) and the mixture was cooled to -50 ^{0}C by means of an acetonitrile dry ice bath. *n*-Butyllithium (57.4 mL of a 1.6 M solution in hexanes, 91.8 mmol) was added dropwise to the reaction and the mixture was allowed to stir for 30 min at -50 ^{0}C. Weinreb amide **565** (19.16 g, 83.4 mmol) was added portionwise via a powder addition funnel. The mixture was allowed to stir at -50 ^{0}C, then warm to rt overnight. When judged to be complete, the reaction was poured into saturated ammonium chloride (500 mL) and stirred vigorously for 30 min. The mixture was then added to a separatory funnel. The organics were collected, washed with water, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow solid (28.64 g) that was pulverized, then triturated with methanol and filtered to give **566** as a pale yellow solid (19.2 g, 68%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.29 (s, 3H), 3.63 (s, 3H), 7.18 (d, 1H), 7.36 (d, 1H), 7.42 (s, 1H), 7.55 (m, 2H), 7.66 (s, 1H).

Step C:

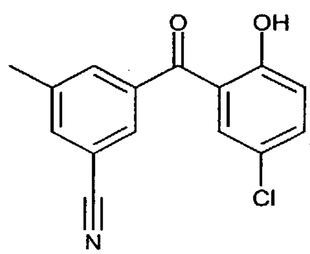


567

Into a oven dried round-bottom flask equipped with a stir bar, nitrogen on demand, and a reflux condenser, were added **566** (4.02 g, 12 mmol), sodium cyanide (1.16 g, 24 mmol),

copper iodide (0.26 g, 1.4 mmol), and propionitrile (50 mL degassed with nitrogen for 30 min). To this mixture was added $Pd(PPh_3)_4$ (Strem, 1.37 g, 1.2 mmol) that had been triturated with methanol and filtered prior to addition. The mixture was heated to reflux and allowed to stir for 30 min. The mixture was cooled to rt and ethyl acetate (100 mL) was added. The resulting suspension was filtered through celite and the solids washed with ethyl acetate. The filtrate was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting product was further purified by flash chromatography using 4:1 hexanes: ethyl acetate to afford **567** as an off-white solid (3.33 g, 99%). ^1H NMR (DMSO-d_6, 300 MHz) δ 2.44 (s, 3H), 3.69 (s, 3H), 7.26 (d, 1H), 7.46 (d, 1H), 7.66 (dd, 1H), 7.86 (d, 2H), 7.99 (s, 1H).

Step D:



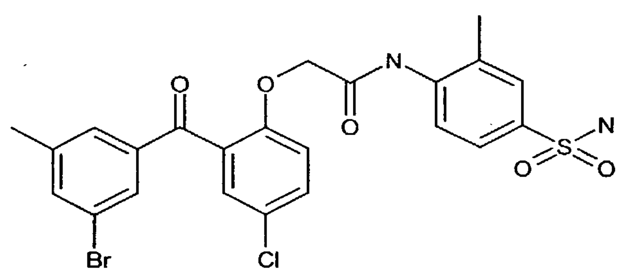
568

Anisole derivative **567** (3.27 g, 14.2 mmol), dichloromethane (45 mL), and boron tribromide (1.41 mL in 15 mL of dichloromethane) were combined as described in general procedure IX. The reaction was stirred at -78 ^{0}C for 1 h then allowed to warm to rt and stir for an additional 4 h. The reaction was then poured into ice water (500 mL) and stirred for additional 45 min, and poured into a separatory funnel. The organic layers were collected and washed with water, brine, and dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow solid (5.62 g). The resulting solid that was recrystallized from methanol and filtered to give **568** as pale yellow crystals (2.65 g, 85%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.4 (s, 3H), 6.98 (d, 1H), 7.37 (d, 1H), 7.47 (dd, 1H), 7.82 (d, 1H), 7.87 (s, 1H), 7.93 (d, 1H), 10.43 (s, 1H).

Step E:

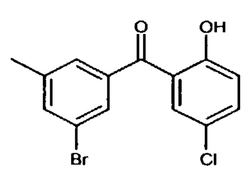
Compound **568** (2.65 g, 9.8 mmol), potassium carbonate (6.74 g, 49 mmol), compound **470** (3.14 g, 10 mmol), and acetone (50 mL) were combined in a round-bottom flask, and heated to reflux for 4 h. The reaction was concentrated in vacuo, then water (200 mL) and dichloromethane were added and the suspension was filtered. The filtrate was poured in a separatory funnel and separated. The organic layer was collected, washed with saturated sodium bicarbonate solution, water, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting solid was further purified by flash chromatography using 1:1 hexanes:ethyl acetate as eluant to afford an off-white solid. The solid was recrystallized from acetonitrile and water to afford **564** (1.61 g, 66%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.17 (s, 3H), 2.37 (s, 3H), 4.81 (s, 2H), 7.24 (m, 3H), 7.5 (d, 1H), 7.58-7.66 (m, 4H), 7.92 (d, 2H), 7.98 (s, 1H), 9.39 (s, 1H).

Example 233:



569

Step A:



570

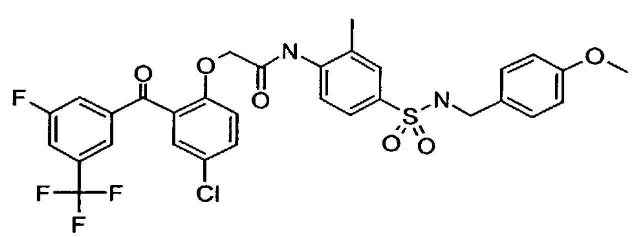
Anisole derivative **566** (1.02 g, 3 mmol), dichloromethane (10 mL), and boron tribromide (3 mL of a 1 M solution in dichloromethane) were combined as described in general procedure IX. The reaction was stirred at -78 ^{0}C for 90 min, and was then allowed to warm to rt and stir for an additional 1 h. Water (100 mL) was added to the reaction and

the resulting mixture was stirred for 30 min. The mixture was then added to a separatory funnel, the organic layer was collected, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **570** as a pale yellow solid (0.965 g, 99%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.34 (s, 3H), 6.96 (d, 1H), 7.33 (d, 1H), 7.45 (m, 2H), 7.58 (s, 1H), 7.69 (s, 1H), 10.37 (s, 1H).

Step B:

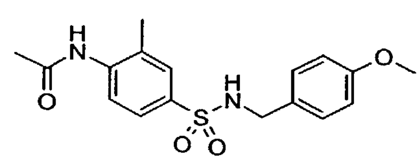
Compound **570** (0.16 g, 0.5 mmol), potassium carbonate (0.34 g, 2.5 mmol), compound **470** (0.166 g, 0.54 mmol), and acetone (5 mL) were combined in a round-bottom flask, and heated to reflux overnight. Water was added, the resulting suspension was filtered and the solids purified by flash chromatography using 9:1 CH_2Cl_2:CH_3OH as eluant to afford **569** as an off-white solid (0.035 g, 13%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.16 (s, 3H), 2.3 (s, 3H), 4.8 (s, 2H), 7.24 (m, 3H), 7.46 (d, 1H), 7.58-7.68 (m, 6H), 9.29 (s, 1H).

Example 234:



571

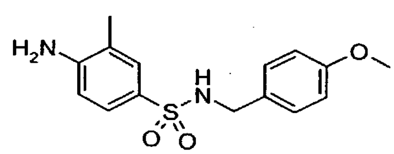
Step A:



572

Sulfonyl chloride **464** (3 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and 4-methoxybenzylamine (Aldrich, 0.41 g, 3.01 mmol). The mixture was allowed to stir for 2 d and was then concentrated in vacuo. Water was added to the remaining residue and the mixture was filtered. The filtrate was extracted with dichloromethane, the organic layer was collected, dried over $MgSO_4$, filtered and concentrated in vacuo to afford the protected sulfonamide **572** (0.16 g, 46%). ^1H NMR (DMSO-d_6, 400 MHz) δ 2.06 (s, 3H), 2.21 (s, 3H), 3.65 (s, 3H), 3.83 (d, 2H), 6.77 (dd, 2H), 7.08 (d, 2H), 7.52 (m, 2H), 7.7 (m, 1H), 7.87 (t, 1H), 9.36 (s, 1H); LC-MS (ES^+) *m/z* 349 $(M+H)^+$, LC-MS (ES^-) *m/z* 347 $(M-H)^-$.

Step B:



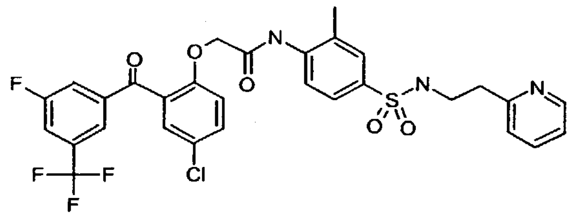
573

The sulfonamide was then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solution was concentrated in vacuo to afford **573**, which was used without further purification.

Step C:

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **573** (0.1 g, 0.33 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solution was concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **571** (0.070 g, 32%). ^1H NMR (DMSO-d_6, 300 MHz) δ 2.15 (s, 3H), 3.69 (s, 3H), 3.87 (d, 2H), 4.82 (s, 2H), 6.8 (m, 2H), 7.1 (d, 2H), 7.23 (d, 1H), 7.56 (dd, 3H), 7.67 (m, 2H), 7.87-8.03 (m, 4H), 9.41 (s, 1H); LC-MS (ES^-) *m/z* 663 $(M-H)^-$.

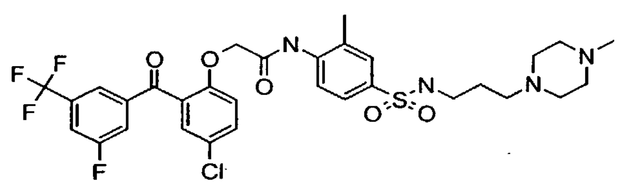
Example 235:



574

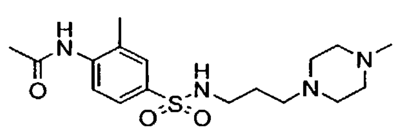
Acid **71** was converted to the acid chloride using the general procedure V. Aniline **527** (0.1 g, 0.34 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **574** (0.040 g, 18%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.16 (s, 3H), 2.8 (dd, 2H), 3.08 (m, 2H), 4.81 (s, 2H), 7.16-7.25 (m, 3H), 7.53-7.69 (m, 7H), 7.88 (m, 2H), 8 (m, 1H), 8.42 (m, 1H), 9.4 (s, 1H); LC-MS (ES$^+$) *m/z* 650 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 648 (M-H)$^-$.

<u>Example 236:</u>



575

Step A:

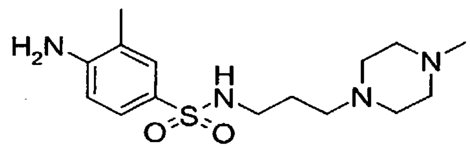


576

Sulfonyl chloride **464** (3 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and 1-(3-aminopropyl)-4-methylpiperazine (Aldrich, 0.48 g, 3.05 mmol). The mixture was allowed to stir for 2 d, followed by concentration in vacuo. Water was

added to the remaining residue and the mixture was filtered. The filtrate was extracted with dichloromethane and the organic layer was collected, dried over $MgSO_4$, filtered and concentrated in vacuo to afford the protected sulfonamide **576** (0.22 g, 20%), which was used without further purification.

Step B:



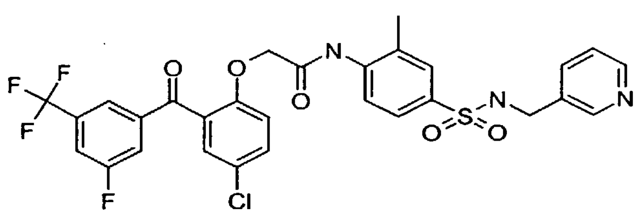
577

The sulfonamide **576** was then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solutions were concentrated in vacuo to afford **577.** The resulting product was used without further purification.

Step C:

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **577** (0.1 g, 0.31 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **575** (0.067 g, 32%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.47 (m, 2H), 2.04-2.21 (m, 16H), 2.73 (m, 2H), 4.82 (s, 2H), 7.23 (d, 1H), 7.45-7.7 (m, 6H), 7.87 (m, 2H), 8.01 (m, 1H), 9.41 (s, 1H); LC-MS (ES$^+$) *m/z* 685 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 683 (M-H)$^-$.

Example 237:

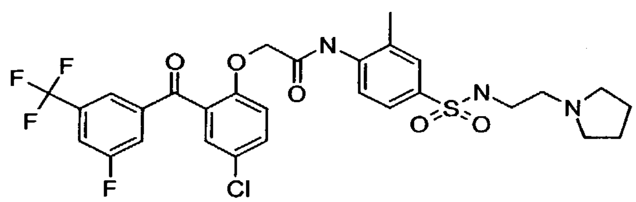


578

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **538** (0.1 g, 0.36 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid

chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **77** (0.053 g, 23%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.16 (s, 3H), 4 (d, 2H), 4.82 (s, 2H), 7.22-7.31 (m, 2H), 7.55-7.7 (m, 6H), 7.88 (d, 2H), 8.02 (m, 1H), 8.12 (t, 1H), 8.41 (dd, 2H), 9.42 (s, 1H); LC-MS (ES$^+$) *m/z* 636 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 634 (M-H)$^-$.

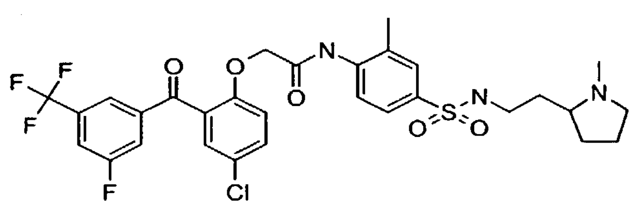
Example 238:



579

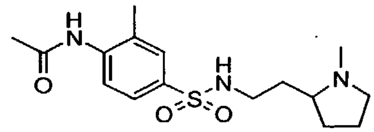
Acid **71** was converted to the acid chloride using the general procedure V. Aniline **515** (0.1 g, 0.35 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.4 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **579** (0.018 g, 8%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6 (m, 4H), 2.17 (s, 3H), 2.3-2.42 (m, 6H), 2.81 (t, 2H), 3.16 (m, 4H), 4.09 (m, 1H), 4.81 (s, 2H), 7.24 (d, 1H), 7.54-7.69 (m, 5H), 7.88 (d, 2H), 8 (d, 1H), 9.41 (s, 1H); LC-MS (ES$^+$) *m/z* 642 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 640 (M-H)$^-$.

Example 239:



580

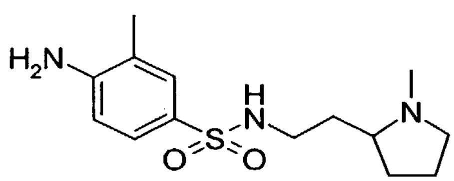
Step A:



581

Sulfonyl chloride **464** (3 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and 2-(2-aminoethyl)-1-methylpyrrolidine (Aldrich, 0.29 g, 2.3 mmol). The mixture was allowed to stir at rt for 2 d, followed by concentration in vacuo. Water was added to the resulting residue and the mixture was filtered. The filtrate was extracted with dichloromethane and the organic layer was collected, dried over $MgSO_4$, filtered and concentrated in vacuo to afford the protected sulfonamide **581** (0.40 g, 51%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.25 (m, 2H), 1.53 (m, 2H), 1.64 (m, 1H), 1.76 (m, 1H), 1.96 (m, 2H), 2.09 (s, 3H), 2.10 (s, 3H), 2.28 (s, 3H), 2.72 (m, 2H), 2.86 (m, 1H), 7.46 (s, 1H), 7.55 (dd, 1H), 7.59 (s, 1H), 7.76 (d, 1H), 9.42 (s, 1H); LC-MS (ES$^+$) *m/z* 340 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 338 (M-H)$^-$.

Step B:



582

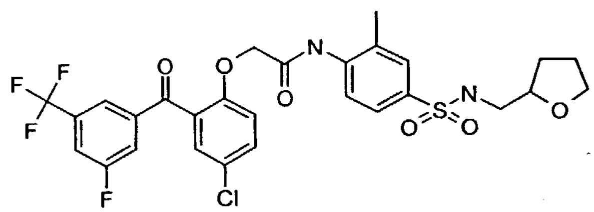
The sulfonamide **581** was then dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solutions were concentrated in vacuo to afford **582**, which was used without further purification.

Step C:

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **582** (0.1 g, 0.34 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by

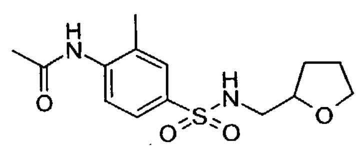
flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **580** (0.037 g, 17%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.25 (m, 2H), 1.47-1.8 (m, 4H), 1.99 (m, 2H), 2.1 (s, 3H), 2.17 (s, 3H), 2.73 (m, 2H), 2.9 (m, 1H), 4.81 (s, 2H), 7.24 (d, 1H), 7.46-7.69 (m, 6H), 7.88 (m, 2H), 8 (m, 1H), 9.41 (s, 1H); LC-MS (ES$^+$) *m/z* 656 (M+H)$^+$.

Example 240:



583

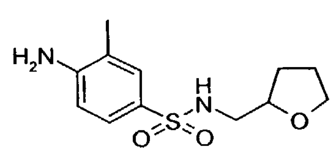
Step A:



584

Sulfonyl chloride **464** (3 mmol) was added portionwise to a large test tube with a stir bar, pyridine (5 mL), and tetrahydrofurfurylamine (Aldrich, 0.41 g, 3.01 mmol). The mixture was allowed to stir at rt for 2 d, followed by concentration in vacuo. Water was added and the mixture was filtered to afford **584** (0.2 g, 64%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.45 (m, 1H), 1.7 (m, 3H), 2.05 (s, 3H), 2.23 (s, 3H), 2.69 (t, 2H), 3.51 (m, 1H), 3.62 (m, 1H), 3.72 (m, 1H), 7.5-7.56 (m, 3H), 7.69 (d, 1H), 9.37 (s, 1H); LC-MS (ES$^+$) *m/z* 313 (M+H)$^+$, LC-MS (ES$^-$) *m/z* 311 (M-H)$^-$.

Step B:



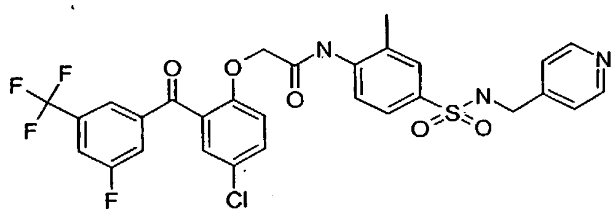
585

Sulfonamide **584** was dissolved in ethanol (10 mL) and 1.5 N HCl (10 mL) and heated to 60 °C overnight. The resulting solution was concentrated in vacuo to afford **585**, which was used without further purification.

Step C:

Acid **71** was converted to the acid chloride using the general procedure V. Aniline **585** (0.1 g, 0.37 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **583** (0.038 g, 16%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.69-1.88 (m, 3H), 2.17 (s, 3H), 2.73 (t, 2H), 3.51-3.81 (m, 3H), 4.81 (s, 2H), 7.24 (d, 2H), 7.54-7.69 (m, 6H), 7.88 (m, 2H), 8.01 (m, 1H), 9.41 (s, 1H); LC-MS (AP$^+$) m/z 629 $(M+H)^+$, LC-MS (AP$^-$) m/z 628 $(M-H)^-$.

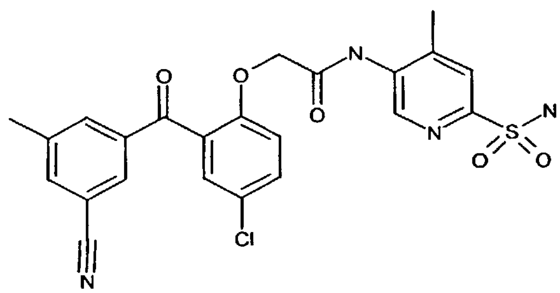
<u>Example 241:</u>



586

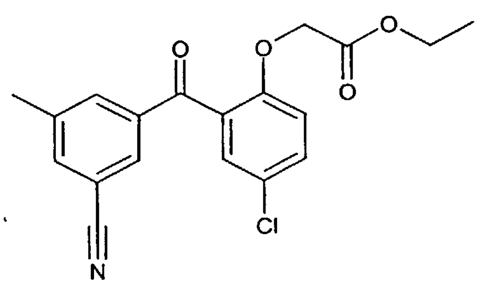
Acid **71** was converted to the acid chloride using the general procedure V. Aniline **541** (0.1 g, 0.36 mmol), acetone (4 mL), sodium bicarbonate (0.22 g, 2.6 mmol), and the acid chloride (0.16 g, 0.40 mmol) were used as in general procedure VI. After 2 d, the resulting solutions were concentrated, re-dissolved in dichloromethane and purified by flash chromatography using 98:2 CH_2Cl_2:CH_3OH as eluant to afford **586** (0.033 g, 14%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.16 (s, 3H), 4 (d, 2H), 4.82 (s, 2H), 7.24 (m, 3H), 7.55-7.7 (m, 5H), 7.89 (m, 2H), 8.02 (m, 1H), 8.20 (t, 1H), 8.44 (dd, 2H), 9.42 (s, 1H); MS (ES$^+$) m/z 636 $(M+H)^+$.

<u>Example 242:</u>



587

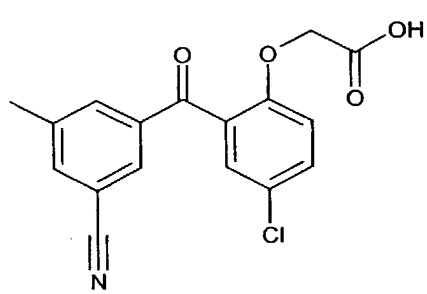
Step A:



588

Compound **568** (2 g, 7.4 mmol), potassium carbonate (5.11 g, 37 mmol), ethyl bromoacetate (1 mL, 9 mmol), and acetone (40 mL) were used as in general procedure II to afford **588** as a yellow/off-white solid (2.73 g, crude material). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.14 (t, 3H), 2.39 (s, 3H), 4.08 (m, 2H), 4.78 (s, 2H), 7.14 (d, 1H), 7.47 (d, 1H), 7.58 (d, 1H), 7.9 (m, 3H).

Step B:



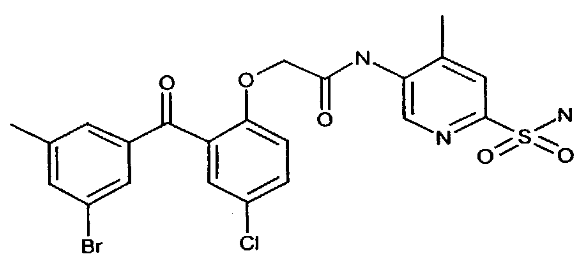
589

Ester **588** (2.73 g, 7.6 mmol), ethanol (EtOH, 20 mL), water (5 mL), and lithium hydroxide monohydrate (0.45 g, 10.7 mmol) were used as in general procedure III to afford **589** as an orange glass (2.45 g, 97%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.3 (s, 3H), 4.67 (s, 2H), 7.1 (d, 1H), 7.44 (d, 1H), 7.58 (dd, 1H), 7.9 (m, 3H), 13.1 (bs, 1H).

Step C:

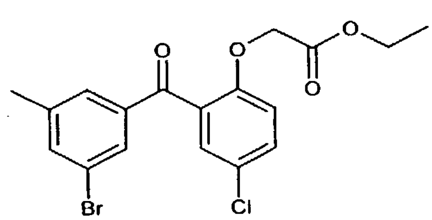
Carboxylic acid **589** (0.1 g, 0.3 mmol), oxalyl chloride (0.4 mL of 2.0 M solution in dichloromethane, 0.8 mmol), DMF (2 drops), and dichloromethane (2 mL), were used according to general procedure V. The acid chloride was dissolved in acetone and added dropwise to aniline **490** (0.086 g, 0.47 mmol), acetone (10 mL), sodium bicarbonate (0.15 g, 1.8 mmol), and water (2 drops) as in general procedure VI. After 4 d, the reaction mixture was concentrated and the product was purified by flash chromatography using 9:1 CH_2Cl_2:CH_3OH as eluant to afford **587** (0.046 g, 31%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.24 (s, 3H), 2.38 (s, 3H), 4.85 (s, 2H), 7.24 (d, 1H), 7.39 (s, 2H), 7.49 (d, 1H), 7.65 (dd, 1H), 7.81 (s, 1H), 7.95 (m, 3H), 8.7 (s, 1H), 9.71 (s, 1H).

Example 243:



590

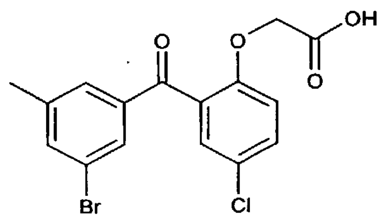
Step A:



591

Compound **570** (0.75 g, 2.3 mmol), potassium carbonate (1.7 g, 12.3 mmol), ethyl bromoacetate (0.3 mL, 2.7 mmol), and acetone (10 mL) were used as in general procedure II to afford **591** as a clear low melting point solid (0.87 g, 92%). The crude product was used without further purification.

Step B:



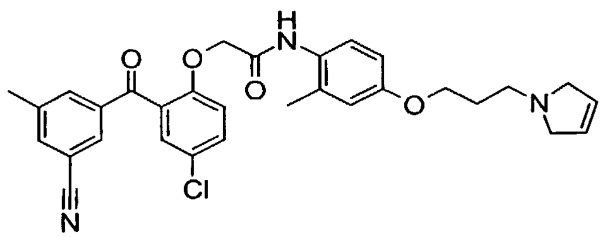
592

Ester **591** (0.87 g, 2.1 mmol), ethanol (EtOH, 7.5 mL), water (2.5 mL), and lithium hydroxide monohydrate (0.125 g, 2.98 mmol) were used as in general procedure III to afford **592** as an white foam (0.74 g, 91%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.32 (s, 3H), 4.68 (s, 2H), 7.08 (d, 1H), 7.41 (d, 1H), 7.57 (d, 2H), 7.67 (s, 2H), 13.1 (bs, 1H).

Step C:

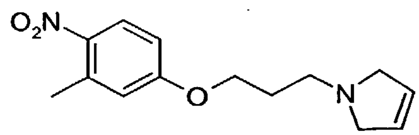
Carboxylic acid **592** (0.1 g, 0.26 mmol), oxalyl chloride (0.4 mL of 2.0 M solution in dichloromethane, 0.8 mmol), DMF (2 drops), and dichloromethane (2 mL), were according to general procedure V. The acid chloride was then dissolved in acetone and added dropwise to aniline **490** (0.086 g, 0.47 mmol), acetone (10 mL), sodium bicarbonate (0.15 g, 1.8 mmol), and water (2 drops) as in general procedure VI. After 5 d, the reaction mixture was concentrated, and the product was purified by flash chromatography using 9:1 CH_2Cl_2:CH_3OH as eluant to afford a solid. The solid was dissolved in dichloromethane, washed with saturated sodium bicarbonate, dried over $MgSO_4$, filtered, and concentrated in vacuo to give **590** (0.029 g, 20%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.19 (s, 3H), 2.3 (s, 3H), 4.75 (s, 2H), 7.22 (d, 2H), 7.43 (d, 2H), 7.58-7.74 (m, 6H), 8.68 (s, 1H).

<u>Example 244:</u>



593

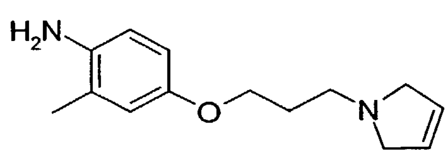
Step A:



594

4-(3-bromo-propoxy)-2-methyl-1-nitrobenzene (3.29 g, 12 mmol), DMF (30 mL), and potassium carbonate (7.6 g, 55 mmol) were combined in a round-bottom flask. 3-Pyrroline (Aldrich, 1 g, 14.5 mmol) was added dropwise to the reaction and the resulting solution was stirred at rt overnight. Water was added to the mixture and the resulting mixture was extracted with ethyl acetate. The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **594** as an orange oil (1.22 g, 39%). ^1H NMR (DMSO-d_6, 400 MHz) δ 1.88 (m, 2H), 2.54 (s, 3H), 2.69 (m, 2H), 3.4 (s, 4H), 4.14 (t, 2H), 5.78 (s, 2H), 6.96 (dd, 1H), 7.03 (d, 1H), 8.03 (d, 1H).

Step B:



595

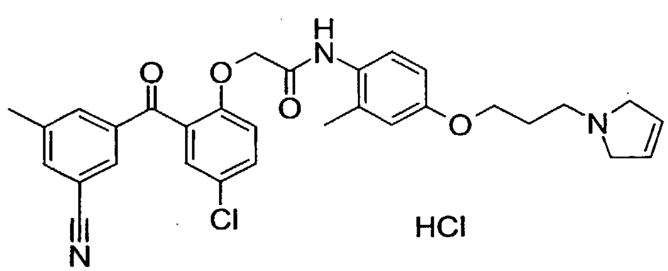
Compound **594** (0.65 g, 2.5 mmol), tin dichloride dihydrate (1.83 g, 8.1 mmol), and ethanol (10 mL) were combined and stirred overnight at rt. Sodium hydroxide (2N) was added and the mixture was extracted with ethyl acetate. The organic layer was collected, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **595** as a brown oil (0.26 g, 49%). ^1H NMR (DMSO-d_6, 300 MHz) δ 1.78 (m, 2H),

2 (s, 3H), 2.65 (m, 2H), 3.37 (s, 4H), 3.83 (t, 2H), 4.34 (bs, 2H), 5.76 (m, 2H), 6.49 (s, 2H), 6.54 (d, 1H).

Step C:

Carboxylic acid **589** (0.2 g, 0.6 mmol), oxalyl chloride (1.4 mL of 2.0 M solution in dichloromethane, 2.8 mmol), DMF (1 drops), and dichloromethane (5 mL), were used to according to general procedure V. The resulting acid chloride was dissolved in acetone and added dropwise to aniline **595** (0.26 g, 1.2 mmol), acetone (10 mL), sodium bicarbonate (0.2 g, 2.4 mmol), and water (1 mL) as in general procedure VI. After 5 d, the reaction mixture was concentrated, and the product was purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **593** as an orange glass (0.127 g, 38%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.86 (m, 4H), 2.01 (s, 3H), 2.36 (s, 3H), 2.76 (m, 2H), 3.48 (m, 2H), 3.97 (t, 2H), 4.7 (s, 2H), 5.8 (s, 2H), 6.7 (m, 2H), 7.12 (d, 1H), 7.22 (d, 1H), 7.48 (d, 1H), 7.65 (dd, 1H), 7.94 (d, 2H), 8.99 (s, 1H).

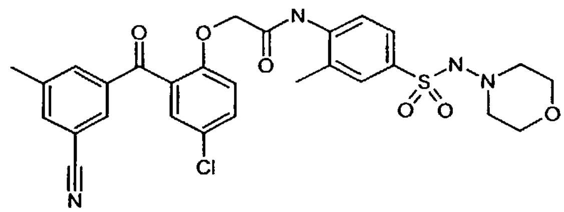
Example 245:



596

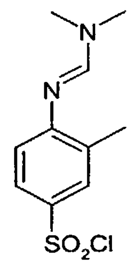
Compound **593** (0.1 g, 0.2 mmol) was dissolved in dioxane (2 mL) and hydrochloric acid (1 mL of a 4M solution in dioxane) was added dropwise. The mixture was allowed to stir for 2 d and was then concentrated in vacuo to afford **596** as a dark solid (0.071 g, 68%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.02 (s, 5H), 2.36 (s, 3H), 3.68 (m, 2H), 3.95 (m, 4H), 4.2 (m, 2H), 4.71 (s, 2H), 5.93 (s, 2H), 6.75 (m, 2H), 7.2 (m, 2H), 7.49 (d, 1H), 7.65 (d, 1H), 7.95 (m, 3H), 9.06 (s, 1H), 10.95 (bs, 1H).

Example 246:



597

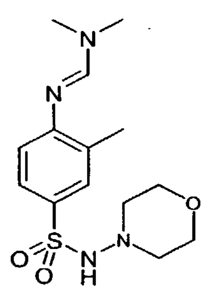
Step A:



598

DMF (59 mL, 762 mmol) was added dropwise to stirred solution of oxalyl chloride (380 mL of a 2M solution in dichloromethane, 760 mmol) in a 1-L 3 neck round-bottom flask at 0 °C. After addition was complete, the reaction was stirred for 1 h then allowed to warm to rt and stir for an additional 2 h. To the resulting white solid was added 2-aminotoluene-5-sulfonic acid (Aldrich, 50 g, 267 mmol) in one portion and the resulting reaction mixture was stirred vigorously for an 1 h. The reaction mixture was transferred to a 1-L round-bottom flask and concentrated to afford **598** as tan solid (150.24 g, crude product). The crude product was carried on without further purification or characterization.

Step B:

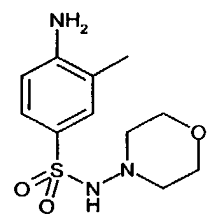


599

Compound **598** (10 g, 38 mmol) was added to a solution of 4-aminomorpholine (Aldrich, 5 g, 49 mmol) in THF (40 mL) and stirred at rt for 2 d. Water and saturated sodium

bicarbonate solution were added and the resulting solution was extracted with ethyl acetate. The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was further purified by flash chromatography using 95:5 CH_2Cl_2:CH_3OH as eluant to afford **599** as an orange glass (0.53 g, crude product). The crude product was used without further purification.

Step C:



600

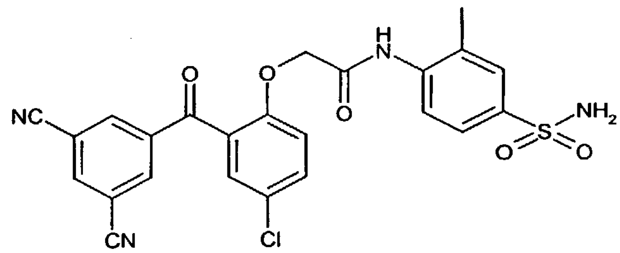
Compound **599** (0.53 g, 1.6 mmol), hydrazine dihydrochloride (0.36 g, 3.4 mmol), and methanol (30 mL) were combined and stirred overnight at rt. The reaction was concentrated in vacuo and the product was purified by flash chromatography using 1:1 hexanes:ethyl acetate as eluant to afford **600** as a white solid (0.075 g, 3.3%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.06 (s, 3H), 2.5 (m, 4H), 3.42 (m, 4H), 5.7 (bs, 2H), 6.62 (d, 1H), 7.34 (m, 2H), 8.23 (s, 1H).

Step D:

Carboxylic acid **589** (0.08 g, 0.24 mmol), oxalyl chloride (0.4 mL of 2.0 M solution in dichloromethane, 0.8 mmol), DMF (1 drops), and dichloromethane (5 mL), were according to general procedure V. The resulting acid chloride was dissolved in acetone and added dropwise to amine **600** (0.07 g, 0.26 mmol), acetone (10 mL), potassium carbonate (0.1 g, 0.72 mmol), and water (1 drop) as in general procedure VI. After 1 d, the reaction mixture was concentrated, suspended in dichloromethane, filtered, then further purified by flash chromatography and TLC prep plate using 98:2 and 95:5 CH_2Cl_2:CH_3OH as eluant respectively to afford and off-white solid. The resulting solid was further triturated in dichloromethane and filtered to afford **597** as a white solid (0.014 g, 10%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H), 2.50 (s, 3H), 2.66 (m, 4H), 3.64 (m, 4H), 4.74 (s, 2H), 5.26 (s, 1H), 7.08 (d, 1H), 7.35 (d, 1H), 7.59 (dd, 1H), 7.72 (s, 1H), 7.85

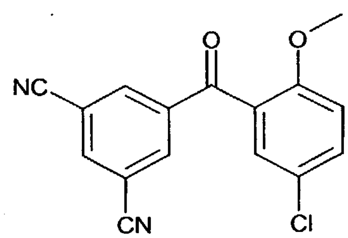
(m, 4H), 8.19 (d, 1H), 8.69 (s, 1H); LC-MS (AP$^+$) *m/z* 583 (M+H)$^+$, LC-MS (AP$^-$) *m/z* 581 (M-H)$^-$.

Example 247:



601

Step A:

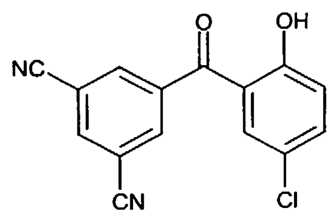


602

Compound **623** (0.5 g, 1.2 mmol), copper (I) cyanide (Aldrich, 0.55 g, 6.1 mmol), pyridine (4 mL, 49.5 mmol), and DMF (15 mL) were combined in a pressure tube equipped with a stir bar, nitrogen on demand, and a reflux condenser. The mixture was allowed to stir at reflux temperature for 4 d. The mixture was cooled, diethyl ether (150 mL) was added, the resulting suspension was filtered through celite and washed with diethyl ether (3 X 150 mL). The filtrate was washed with 2:1 water:concentrated ammonium hydroxide, saturated ammonium chloride, and saturated sodium bicarbonate. The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was further purified by flash chromatography using 4:1 hexanes:CH_2Cl_2 as eluant to afford **602** as an

off-white solid (0.13 g, 35%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.65 (s, 3H), 7.25 (d, 1H), 7.48 (d, 1H), 7.66 (dd, 1H), 8.4 (d, 2H), 8.71 (s, 1H); GC-MS (EI$^+$) *m/z* 296 (M)$^+$.

Step B:



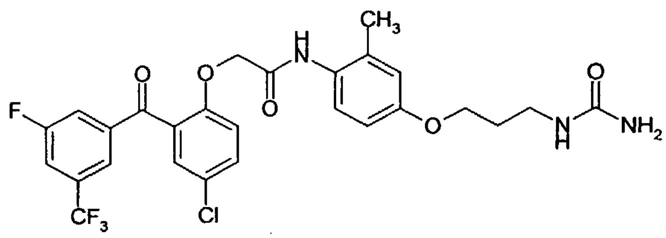
603

Anisole derivative **602** (0.125 g, 0.42 mmol), dichloromethane (10 mL), and boron tribromide (0.44 mL of a 1 M solution in dichloromethane) were combined as described in general procedure IX. The reaction was stirred at -78 ^{0}C for 1 h and was then allowed to warm to rt and stir for an additional 1 h. Water (50 mL) was added to the solution and the resulting mixture was stirred vigorously for 15 min, after which time it was added to a separatory funnel. The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated in vacuo to give **603** as a yellow glass (0.12 g, 99%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7 (d, 1H), 7.45 (d, 1H), 7.52 (dd, 1H), 8.42 (d, 2H), 8.7 (m, 1H); GC-MS (EI$^+$) *m/z* 282 (M)$^+$

Step C:

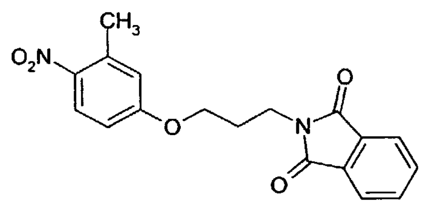
Compound **603** (0.13 g, 0.46 mmol), potassium carbonate (0.12 g, 0.87 mmol), compound **470** (0.146 g, 0.42 mmol), and acetone (5 mL) were combined in a round-bottom flask and stirred at rt overnight. Water (20 mL) was added and the suspension was filtered and the resulting solids were washed with diethyl ether and air dried to afford **601** as an off-white solid (0.212 g, 98%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.19 (s, 3H), 4.82 (s, 2H), 7.24 (m, 3H), 7.51-7.74 (m, 3H), 8.5 (d, 2H), 8.69 (m, 1H), 9.5 (s, 1H); LC-MS (AP$^+$) *m/z* 508 (M+H)$^+$, LC-MS (AP$^-$) *m/z* 506 (M-H)$^-$.

Example 248:



604

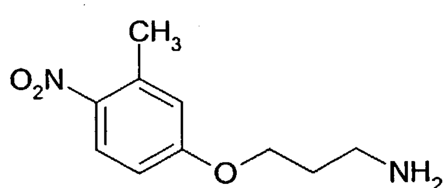
Step A:



605

3-Methyl-4-nitrophenol (Aldrich, 5.0 g, 33 mmol), 3-bromopropyl phthalimide (8.8 g , 33 mmol), Cs_2CO_3 (16.1 g, 5.0 mmol), and anhydrous DMF (60 mL) were added to a round bottom flask and heated to 55 °C for 2 h. The reaction was then allowed to cool to rt and was poured into a mixture of Et_2O and water. The resulting solid was filtered, washed with water and Et_2O, and allowed to dry in a vacuum oven at 45 °C for 12-16 h to provide **605** (9.5 g, 85 %) as a tan solid: ^1H NMR (DMSO-d_6, 300 MHz) δ 8.03 (m, 1H), 7.87 (m, 4H), 6.87 (m, 2H), 4.16 (t, 2H), 3.79 (t, 2H), 2.51 (s, 3H), 2.11 (m, 2H).

Step B:

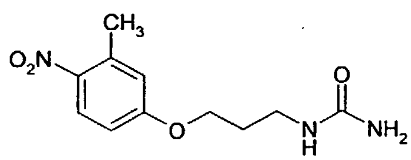


606

Into a round bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand were added **605** (3.0 g, 8.8 mmol), hydrazine hydrate (1.6 mL, 1.7 g, 53 mmol),

and absolute ethanol (50 mL). The reaction was heated to reflux and allowed to stir for 4 h, after which time the reaction mixture was allowed to cool to rt and stir for an additional 48-60 h. The resulting heterogenous mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting solid was washed with CH_2Cl_2, filtered and dissolved in ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to provide **606** (1.1 g, 59%) as a yellow oil: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.99 (d, 1H), 6.97 (d, 1H), 6.91 (dd, 1H), 4.10 (t, 2H), 2.63 (t, 2H), 2.49 (s, 3H), 1.77 (m, 2H).

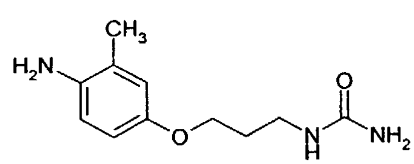
Step C:



607

Into a round bottom flask equipped with a stir bar and nitrogen on demand were added **606** (0.3 g, 1.43 mmol), anhydrous THF (5 mL), and trimethylsilyl isocyanate (0.21 mL, 0.18 g, 1.57 mmol). The mixture was allowed to stir at rt for 3 h, after which time water (1mL) was added to the heterogeneous solution. The mixture was concentrated under reduced pressure and the resulting residue was washed with a mixture of ethyl acetate and Et_2O, filtered, and dried to afford **607** (0.273 g, 75%) as a pale yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.00 (d, 1H), 6.97 (d, 1H), 6.90 (dd, 1H), 5.97 (t, 1H), 5.35 (bs, 2H), 4.04 (t, 2H), 3.05 (m, 2H), 2.44 (s, 3H), 1.77 (m, 2H).

Step D:



608

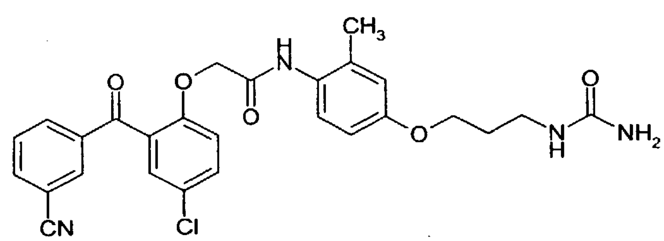
To a flask equipped with a stir bar were added **607** (0.055 g, 0.22 mmol), ethanol (8 mL), and palladium on carbon (0.006 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 40 p.s.i. When judged to be complete, the reaction mixture was filtered through celite and the solvents were removed under reduced pressure

to provide **608** (0.045 g, 92%) as a white solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.51 (s, 1H), 6.46 (m, 2H), 5.92 (t, 1H), 5.33 (bs, 2H), 4.30 (bs, 2H), 3.75 (t, 2H), 3.03 (m, 2H), 1.96 (s, 3H), 1.67 (m, 2H).

Step E:

Acid **71** (0.17 g, 0.45 mmol), oxalyl chloride (0.25 mL of a 2 M solution in CH_2Cl_2, 0.50 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline **608** (0.95 g, 0.43 mmol), $NaHCO_3$ (0.19 g, 2.3 mmol), acetone (5 mL), and water (1 mL) were used according to general procedure VI. The resulting solid was washed with Et_2O, filtered, and dried in vacuo at 50 °C to afford **604** (0.115 g mg, 44 %) as a white solid: MS (ES+) *m/z* 581 (M^+); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.10 (s, 1H), 8.01 (d, 1H), 7.86 (m, 2H), 7.67 (dd, 1H), 7.54 (d, 1H), 7.22 (d, 1H), 7.08 (d, 1H), 6.75 (d, 1H), 6.69 (dd, 1H), 5.98 (t, 1H), 5.37 (bs, 2H), 4.70 (s, 2H), 3.91 (t, 2H), 3.08 (q, 2H), 1.99 (s, 3H), 1.76 (m, 2H).

Example 249:

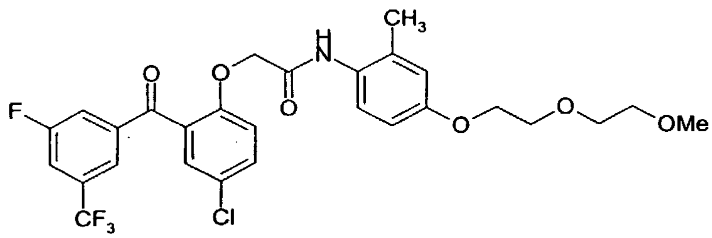


609

Step A:

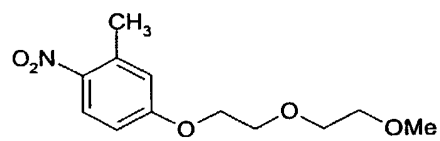
Acid **129** (0.14 g, 0.45 mmol), oxalyl chloride (0.25 mL of a 2 M solution in CH_2Cl_2, 0.50 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline **608** (0.095 g, 0.43 mmol), $NaHCO_3$ (0.19 g, 2.3 mmol), acetone (5 mL), and water (1 mL) were used according to general procedure VI. The resulting residue was treated with Et_2O and a solid precipitated. The solid was purified by flash chromatography using 5% MeOH:CH_2Cl_2 to afford **609** (0.015 g, 6%) as a white solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.01 (s, 1H), 8.13 (s, 1H), 8.03 (m, 2H), 7.63 (m, 2H), 7.47 (d, 1H), 7.18 (d, 1H), 7.07 (d, 1H), 6.72 (d, 1H), 6.65 (dd, 1H), 5.94 (m, 1H), 5.34 (bs, 2H), 4.65 (s, 2H), 3.87 (t, 2H), 3.03 (m, 2H), 1.95 (s, 3H), 1.76 (m, 2H).

Example 250:



610

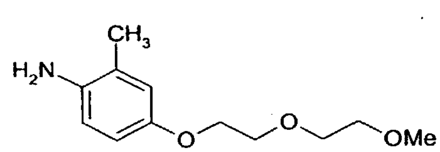
Step A:



611

To a round bottom flask equipped with a stir bar and nitrogen on demand were added 5-fluoro-2-nitrotoluene (1.0 g, 6.45 mmol), di(ethylene glycol) methyl ether (0.77 mL, 0.77 g, 6.45 mmol), anhydrous DMF (20 mL), and K_2CO_3 (1.8 g, 12.9 mmol). The reaction mixture was heated to 80 °C and allowed to stir for 16-18 h, after which time additional di(ethylene glycol) methyl ether (1.15 mL, 1.16 g , 9.67 mmol) was added. The reaction was heated to 130 °C and allowed to stir for 16-18 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into ethyl acetate and water. The organic layer was washed with 5% NaOH aqueous solution, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford **611** (1.07 g, 65%) as a yellow oil: ^1H NMR (DMSO-d_6, 300 MHz) δ 8.06 (d, 1H), 7.08 (d, 1H), 7.01 (dd, 1H), 4.24 (t, 2H), 3.78 (t, 2H), 3.60 (m, 2H), 3.48 (m, 2H), 3.27 (s, 3H), 2.57 (s, 3H).

Step B:



612

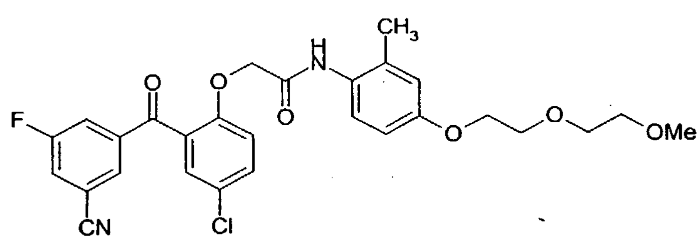
To a flask equipped with a stir bar were added **611** (0.36 g, 1.4 mmol), ethanol (10 mL), and palladium on charcoal (0.036 g of 10% Pd/C, 10% by weight). The vessel was placed on a hydrogenation apparatus at 43 p.s.i for 2 h, after which time the reaction mixture was filtered through celite. To the filtrate were added 1N HCl and ethyl acetate. The layers were separated and the pH of the aqueous layer was adjusted using saturated $NaHCO_3$.

The aqueous layer was extracted with ethyl acetate, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to provide **612** (0.18 g, 57%) as a yellow oil: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.52 (s, 1H), 6.46 (s, 1H), 4.32 (bs, 2H), 3.86 (t, 2H), 3.60 (m, 2H), 3.50 (m, 2H), 3.39 (m, 2H), 3.19 (s, 3H), 1.96 (s, 3H).

Step C:

Acid **71** (0.16 g, 0.42 mmol), oxalyl chloride (0.04 mL, 0.058 g, 0.46 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline **612** (0.09 g, 0.40 mmol), $NaHCO_3$ (0.176 g, 2.1 mmol), acetone (7 mL), and water (1 mL) were used according to general procedure VI. The resulting residue was treated with diethyl ether to afford **610** (0.061 g, 25%) as a white solid: MS (ES+) *m/z* 584 (M^+); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.06 (s, 1H), 7.97 (d, 1H), 7.82 (m, 2H), 7.63 (dd, 1H), 7.49 (d, 1H), 7.18 (d, 1H), 7.05 (d, 1H), 6.73 (s, 1H), 6.66 (dd, 1H), 4.66 (s, 2H), 3.98 (t, 2H), 3.65 (t, 2H), 3.52 (m, 2H), 3.40 (m, 2H), 3.19 (s, 3H), 1.95 (s, 3H).

Example 251:



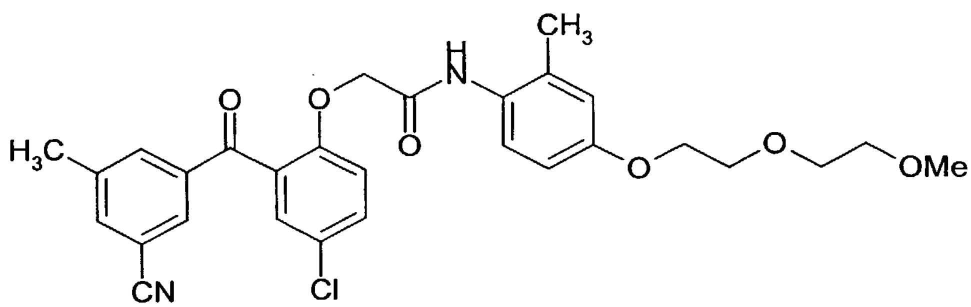
613

Step A:

Acid **496** (0.1 g, 0.3 mmol), oxalyl chloride (0.03 mL, 0.042 g, 0.33 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline **612** (0.065 g, 0.29 mmol), $NaHCO_3$ (0.126 g, 1.5 mmol), acetone (10mL), and water (0.5 mL) were used according to general procedure VI. The product was purified by flash chromatography using 2% MeOH:CH_2Cl_2 as eluant and then rechromatographed using 1:1 hexanes:ethyl acetate as eluant. Upon standing, crystals formed in the collected fractions. The crystals were collected and dried to afford **613** (0.012 g, 7 %) a pink crystalline solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.08 (s, 1H), 8.09 (d, 1H), 7.99 (s, 1H), 7.87 (d, 1H), 7.63 (dd, 1H), 7.48

(d, 1H), 7.17 (d, 1H), 7.08 (d, 1H), 6.74 (d, 1H), 6.67 (dd, 1H), 4.67 (s, 2H), 3.99 (t, 2H), 3.65 (t, 2H), 3.51 (m, 2H), 3.40 (m, 2H), 3.19 (s, 3H), 1.95 (s, 3H).

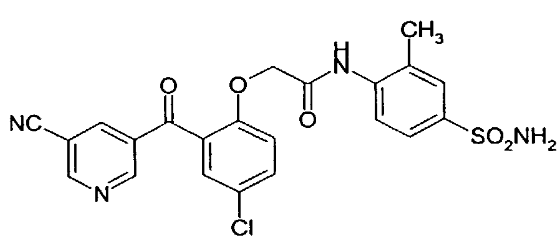
Example 252:



614

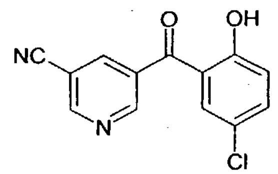
Acid **589** (0.138 g, 0.42 mmol), oxalyl chloride (0.04 mL, 0.058 g, 0.46 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline **612** (0.09 g, 0.40 mmol), $NaHCO_3$ (0.176 g, 2.1 mmol), acetone (7 mL), and water (1 mL) were used according to general procedure VI. The product was purified by flash chromatography using 1:1 hexanes: ethyl acetate as eluant and subsequently treated with Et_2O to afford **614** (0.048 g, 21%) as a beige solid: MS (ES+) *m/z* 537 (M^+); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.95 (s, 1H), 7.92 (s, 1H), 7.86 (m, 2H), 7.61 (dd , 1H), 7.45 (d, 1H), 7.18 (d, 1H), 7.08 (d, 1H), 6.74 (s, 1H), 6.67 (m, 1H), 4.66 (s, 2H), 3.99 (t, 2H), 3.65 (t, 2H), 3.51 (q, 2H), 3.40 (q, 2H), 3.19 (s, 3H), 2.31(s, 3H), 1.96 (s, 3H).

Example 253:



615

Step A:



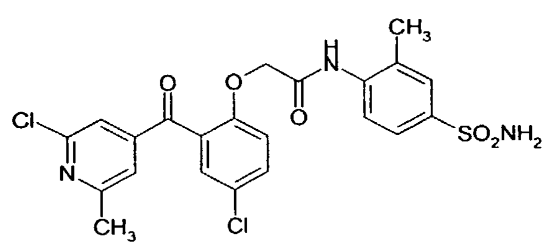
616

To a round bottom flask equipped with a reflux condenser, stir bar, and nitrogen on demand were placed **44** (0.45 g, 1.44 mmol), copper (I) cyanide (0.32 g, 3.6 mmol), and anhydrous DMF (20 mL). The reaction mixture was heated to reflux and allowed to stir for 3 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into ethyl acetate and water. The resulting emulsion was filtered, the organic layer was collected, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **616** (0.2 g, 54%) as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.59 (s, 1H), 9.17 (d, 1H), 9.00 (d, 1H), 8.54 (m , 1H), 7.48 (dd, 1H), 7.43 (d, 1H), 6.95 (d, 1H).

Step B:

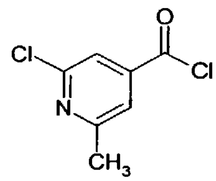
A mixture of **616** (0.20 g, 0.77 mmol), **470** (0.237 g, 0.77 mmol), potassium carbonate (0.213 g, 1.5 mmol), and sodium iodide (230 mg, 1.54 mmol) in 8 mL of acetone was warmed to reflux for 6 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was treated with Et_2O and the resulting solid was filtered and recrystallized from CH_3CN to provide **615** (8 mg, 3%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.48 (s, 1H), 9.20 (d, 1H), 9.13 (d, 2H), 8.64 (t, 1H), 7.64 (m, 5H), 7.25 (m, 3H), 4.81 (s, 2H), 2.17 (s, 3H).

Example 254:



617

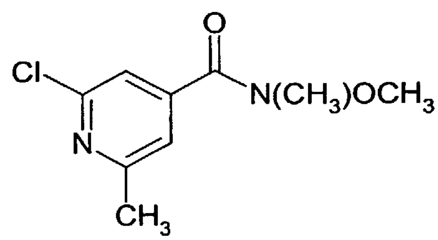
Step A:



618

2- Chloro-6-methylisonicotinic acid (1 g, 5.8 mmol), CH_2Cl_2 (20 mL), oxalyl chloride (0.56 mL, 0.8 g, 6.4 mmol), and N,N-dimethylformamide (1 drop) were used according to general procedure V to afford **618** (1.1g, >99%) as a purple oil. The product was used in the next step without further purification.

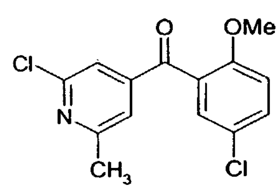
Step B:



619

Acid chloride **618** (1.1 g, 5.8 mmol), N,O-dimethylhydroxylamine hydrochloride (1.1 g, 11.6 mmol), Et_3N (1.6 mL, 1.2 g, 11.6 mmol), and $CHCl_3$ (50 mL) were used according to general procedure VII to provide **619** (1.3 g, >99%) as a purple oil. The product was used in the next step without further purification: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.42 (s, 1H), 7.38 (s, 1H), 3.54 (s, 3H), 3.24 (s, 3H).

Step C:

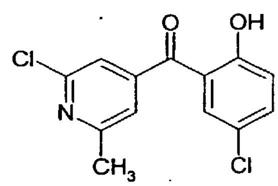


620

Amide **619** (1.3 g, 5.8 mmol), n-butyllithium (4 mL of a 1.6 M solution in hexanes, 6.4 mmol), 2-bromo-4-chloroanisole (0.8 mL, 1.3 g, 5.8 mmol), and diethyl ether (25 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 3:2 hexanes:ethyl acetate as eluant to afford **620** (0.2 g, 12%) as a

pale yellow solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.67 (dd, 1H), 7.50 (d, 1H), 7.42 (s, 1H), 7.38 (s, 1H), 7.24 (d, 1H), 3.65 (s, 3H), 2.51 (s, 3H).

Step D:



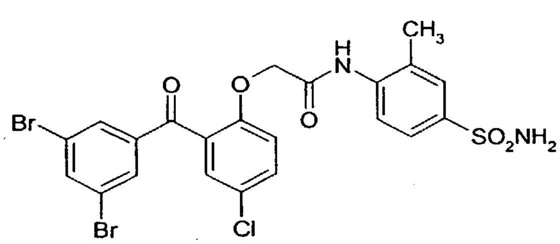
621

Anisole **620** (0.2 g, 0.68 mmol), BBr_3 (1.4 mL of a 1.0 M solution in CH_2Cl_2, 1.4 mmol), and CH_2Cl_2 (5 mL) were used according to general procedure IX to afford **621** (0.163 g, 85%) as a yellow solid. The product was used without further purification: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.56 (s, 1H), 7.47 (dd, 1H), 7.41 (s, 1H), 7.38 (m, 2H), 6.93 (d, 1H), 2.47 (s, 3H).

Step E:

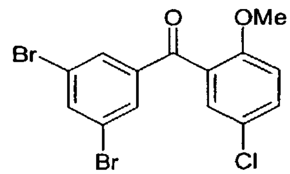
A mixture of **621** (0.08 g, 0.28 mmol), **470** (0.086 g, 0.28 mmol), and potassium carbonate (0.077 g, 0.56 mmol) in 10 mL of acetone was warmed to reflux for 1.5 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was treated with MeOH and the resulting solid was filtered to provide **617** (0.007 g, 5%): MS (ES+) *m/z* 508 (M^+); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.38 (s, 1H), 7.64 (m, 1H), 7.61 (s, 1H), 7.56 (s, 2H), 7.50 (m, 2H), 7.45 (s, 1H), 7.20 (m, 3H), 4.75 (s, 2H), 2.42 (s, 3H), 2.13 (s, 3H).

<u>**Example 255:**</u>



622

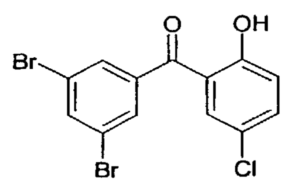
Step A:



623

A solution of 1,3,5-tribromobenzene (3.0 g, 9.53 mmol) in 50 mL of ether was cooled to –78 °C in a dry ice/acetone bath. *n*-Butyllithium (4.2 mL of a 2.5 M solution in hexanes, 10.5 mmol) was added dropwise over 10 min. The resulting mixture was stirred at –78 °C for an additional 10 min, then **183** (2.0 g, 9.53 mmol) was added in small portions over 10 min. The reaction mixture was lifted from the cold bath, allowed to warm to rt and continue stirring for 1.5 h. The mixture was poured into water and extracted with Et_2O. The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting orange residue was treated with MeOH, filtered and dried to provide **623** (2.03 g, 53%) as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.12 (m, 1H), 7.71 (m, 2H), 7.60 (dd, 1H), 7.43 (d, 1H), 7.20 (d, 1H), 3.63 (s, 3H).

Step B:



624

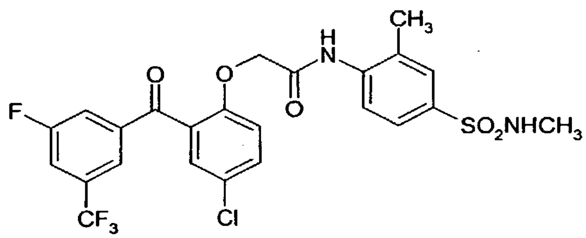
Anisole **623** (0.2 g, 0.49 mmol), BBr_3 (1 mL of a 1.0 M solution in CH_2Cl_2, 1 mmol), and CH_2Cl_2 (8 mL) were used according to general procedure IX to afford **624** (0.176 g, 92%) as a yellow solid. The product was used without further purification: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.46 (s, 1H), 8.10 (m, 1H), 7.74 (m, 2H), 7.43 (dd, 1H), 7.35 (d, 1H), 6.93 (d, 1H).

Step C:

A mixture of **624** (0.12 g, 0.31 mmol), **470** (0.095 g, 0.31 mmol), potassium carbonate (0.086 g, 0.62 mmol), sodium iodide (0.093 g, 0.62 mmol) and 10 mL of acetone were warmed to reflux for 12-16 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue

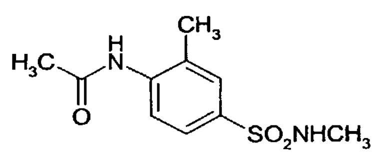
was treated with Et_2O and the resulting solid was filtered and dried to provide **622** (0.04 g, 21%) as a yellow solid: ^1H NMR (DMSO-d_6, 00 MHz) δ 9.35 (s, 1H), 8.07 (t, 1H), 7.83 (m, 2H), 7.60 (m, 4H), 7.47 (d, 1H), 7.20 (m, 3H), 4.77 (s, 2H), 2.14 (s, 3H).

Example 256:



625

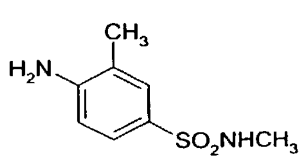
Step A:



626

Into a round bottom flask equipped with a stir bar and gas dispersion tube was added sulfonyl chloride **464** (11.5 g, 0.046 mol) and THF (250 mL) and the mixture was cooled to 0 °C. Methylamine gas was bubbled through the reaction mixture for 0.5 h, after which time, the mixture was poured into EtOAc and water. The pH of the aqueous layer was adjusted to 7 using concentratd HCl. The organic layer was collected, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The resulting orange residue was treated with Et_2O, filtered and dried to provide **626** (5.32 g, 48%): ^1H NMR (DMSO-d_6, 300 MHz) δ 9.46 (s, 1H), 7.80 (d, 1H), 7.58 (m, 2H), 7.34 (m, 1H), 2.41 (d, 3H), 2.32 (s, 3H), 2.13 (s, 3H)

Step B:



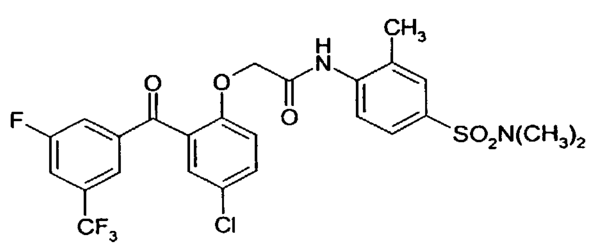
627

Into a round bottom flask equipped with a stir bar, reflux condenser, and nitrogen on demand were placed **626** (6.2 g, 0.026 mol), ethanol (250 mL), and 1.5 N (75 mL). The mixture was warmed to reflux and allowed to stir for 6 h. When judged to be complete, the reaction was allowed to cool to rt and was poured into a cold solution of saturated $NaHCO_3$. The mixture was extracted with several portions of EtOAc and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide **627** (3.6 g, 69%) as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.23 (m, 2H), 6.82 (m, 1H), 6.59 (d, 1H), 5.62 (bs, 2H), 2.26 (d, 3H), 2.03 (s, 3H).

Step C:

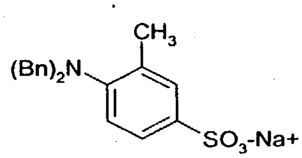
Acid **71** (0.237 g, 0.63 mmol), oxalyl chloride (0.35 mL of a 2 M solution in CH_2Cl_2, 0.69 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V to afford the acid chloride. The acid chloride, aniline **627** (0.12 g, 0.60 mmol), $NaHCO_3$ (0.264 g, 3.2 mmol), acetone (7 mL), and water (1 mL) were used according to general procedure VI. The resulting residue was treated with Et_2O and filtered to afford **625** (0.158 g, 45%) as a white solid: MS (ES+) *m/z* 558 (M^+); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.38 (s, 1H), 7.97 (d, 1H), 7.84 (m, 2H), 7.62 (m, 2H), 7.55 (m, 1H), 7.50 (m, 2H), 7.30 (m, 1H), 7.19 (d, 1H), 4.77 (s, 2H), 2.34 (d, 3H), 2.13 (s, 3H).

Example 257:



628

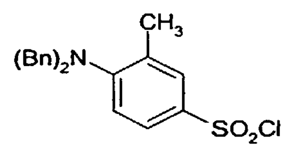
Step A:



629

Into a round bottom flask equipped with a stir bar, reflux condenser and nitrogen on demand was added 2-aminotoluene-5-sulfonic acid (10 g, 0.053 mol), CH_2Cl_2 (120 mL), Na_2CO_3 (22.3 g, 0.21 mol) as a solution in water (120 mL), and the benzyl bromide (14.3 mL, 20.5 g, 0.12 mol). The reaction mixture was warmed to reflux and allowed to stir for 72 h. When judged to be complete, EtOH was added to the reaction mixture and the solvents were removed under reduced pressure to afford **629** (27.4 g, >100%) as a brown oil. The product was used in the next step without further purification.

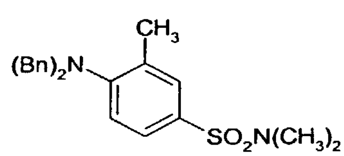
Step B:



630

Into a round bottom flask equipped with a stir bar and nitrogen on demand were added **629** (20.6 g, 0.053 mol) and anhydrous DMF (200 mL). The mixture was cooled to 0 °C and thionyl chloride (11.7 mL, 19.0 g, 0.16 mol) was added dropwise over 15 min, after which time the reaction mixture was allowed to warm to rt and stir for an additional 2 h. When judged to be complete, the mixture was poured into ice water and was allowed to stir for 30 min. The aqueous mixture was extracted with EtOAc and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **630** (5.0 g, 24%). The product was used without further purification.

Step C:

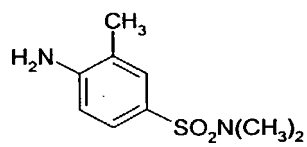


631

Dimethylamine (11.6 mL of a 5.6 M solution in EtOH, 0.065 mol) was placed in a round bottom flask equipped with a stir bar and nitrogen on demand, and cooled to 0 °C. Sulfonyl chloride **630** (5.0 g, 0.013 mol) was added portion-wise over 10 min and the reaction mixture was allowed to stir at 0 °C for 30 min. When judged to be complete, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was collected, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The

product was filtered through a pad of silica gel using CH_2Cl_2 as eluant and the filtrate concentrated under reduced pressure to afford **631** (1.0 g, 20%) as a yellow oil: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.47 (d, 1H), 7.22 (m, 11H), 7.05 (d, 1H), 4.13 (s, 4H), 2.48 (s, 6H), 2.44 (s, 3H).

Step D:



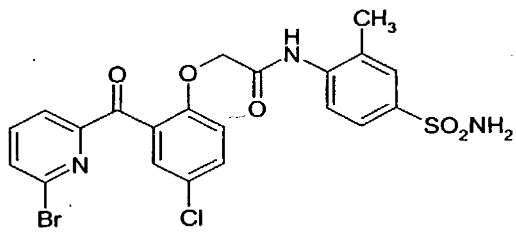
632

To a plastic-coated reaction vessel equipped with a stir bar, was added **631** (0.330 g, 0.85 mmol), toluene (10 mL), and palladium on charcoal (50 mg of 10% by weight Pd/C). The vessel was placed on a hydrogenation apparatus at 40 p.s.i. When the reaction was judged to be complete, it was filtered through celite and the filtrate was washed with saturated $NaHCO_3$ and water. The organic layer was collected, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to provide **632** (120 mg, 67%) as a beige solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.19 (m, 2H), 6.64 (d, 1H), 5.74 (bs, 2H), 2.44 (s, 6H), 2.04 (s, 3H).

Step E:

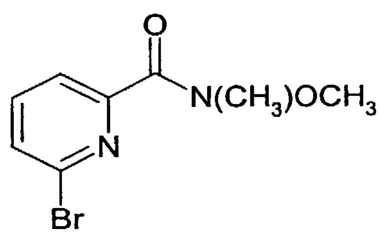
Acid **71** (0.222 g, 0.59 mmol), oxalyl chloride (0.32 mL of a 2 M solution in CH_2Cl_2, 0.65 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline **632** (0.12 g, 0.56 mmol), $NaHCO_3$ (248 mg, 3.0 mmol), acetone (7 mL), and water (1 mL) were used according to general procedure VI. The resulting residue was treated with Et_2O and filtered to afford **628** (0.142 g, 42%) as a white solid: MS (ES+) *m/z* 572 (M^+); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.37 (s, 1H), 7.96 (d, 1H), 7.83 (m, 2H), 7.73 (d, 1H), 7.62 (dd, 1H), 7.50 (m, 3H), 7.19 (d, 1H), 4.78 (s, 2H), 2.53 (s, 6H), 2.17 (s, 3H).

Example 258:



633

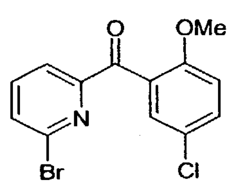
Step A:



634

Picolinic acid (3 g, 0.015 mol), CH_2Cl_2 (50 mL), oxalyl chloride (1.5 mL, 2.2 g, 0.017 mol), and N,N-dimethylformamide (4-5 drops) were used according to general procedure V. The resulting acid chloride, N,O-dimethylhydroxylamine hydrochloride (2.9 g, 0.03 mol), Et_3N (4.2 mL, 3.0 g, 0.03 mol), and $CHCl_3$ (50 mL) were used according to general procedure VII to provide **634** (3.7 g, >99%) as a yellow oil. The product was used without further purification: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.83 (m, 1H), 7.72 (m, 1H), 7.59 (d, 1H), 3.61 (s, 3H), 3.21 (s, 3H).

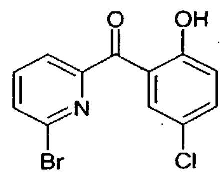
Step B:



635

Amide **634** (3.7 g, 0.015 mol), n-butyllithium (6.4 mL of a 2.5 M solution in hexanes, 0.016 mol), 2-bromo-4-chloroanisole (2.1 mL, 3.3 g, 0.015 mol), and anhydrous diethyl ether (20 mL) were used according to general procedure VIII. The product was purified by flash chromatography using 9:1 hexanes:ethyl acetate as eluant and subsequently recrystallized from MeOH to afford **635** (2.25 g, 46%) as a white solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.90 (m, 3H), 7.55 (dd, 1H), 7.44 (d, 1H), 7.17 (d, 1H), 3.58 (s, 3H).

Step C:



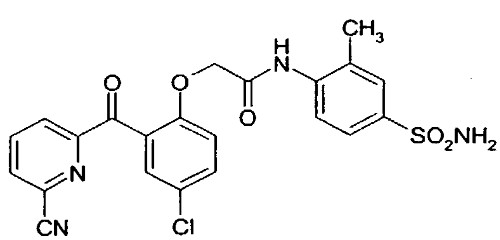
636

Anisole **635** (0.227 g, 0.85 mmol), BBr_3 (1.7 mL of a 1.0 M solution in CH_2Cl_2, 1.7 mmol), and CH_2Cl_2 (15 mL) were used according to general procedure IX to afford **636** (0.069 g, 26%) as a yellow solid. The product was used in the next step without further purification: ^1H NMR (DMSO-d_6, 400 MHz) δ 10.40 (s, 1H), 7.88 (m, 3H), 7.43 (m, 2H), 6.99 (d, 1H).

Step D:

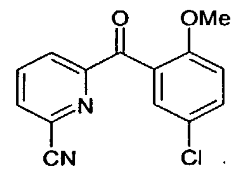
A mixture of **636** (0.07 g, 0.22 mmol), **482** (0.081 g, 0.23 mmol), potassium carbonate (0.061 g, 0.44 mmol) in 10 mL of acetone was heated to reflux. When the reaction was judged to be complete, it was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The resulting solid was washed with warm CH_3CN, filtered and dried to provide **633** (0.027 g, 23%) as a white solid: MS (ES+) *m/z* 540 (M+H); ^1H NMR (DMSO-d_6, 400 MHz) δ 9.23 (s, 1H), 7.88 (m, 3H), 7.56 (m, 5H), 7.23 (m, 3H), 4.66 (s, 2H), 2.09 (s, 3H).

Example 259:



637

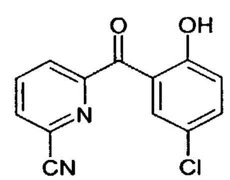
Step A:



638

Into a round bottom flask equipped with a stir bar, nitrogen on demand, and a reflux condenser were added 635 (0.750 g, 2.3 mmol), sodium cyanide (0.225 g, 4.6 mmol), copper (I) iodide (0.078 g, 0.41 mmol), and acetonitrile (10 mL). A stream of nitrogen was bubbled through the reaction mixture for 5 min, after which time tetrakis-(triphenylphosphine)palladium (1.0 g, 0.89 mmol) was added and the mixture was heated to reflux for 2 h. The reaction mixture was allowed to cool to rt and poured into EtOAc and water. The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The orange residue was treated with Et_2O and the resulting solid was filtered and dried to provide 638 (321 mg, 51%) as a pale yellow solid: ^1H NMR (DMSO-d_6, 300 MHz) δ 8.23 (m, 3H), 7.63 (dd, 1H), 7.51 (d, 1H), 7.22 (d, 1H), 3.59 (s, 3H).

Step B:



639

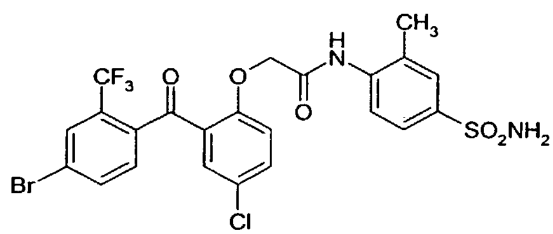
Anisole **638** (0.32 g, 1.17 mmol), BBr_3 (2.3 mL of a 1.0 M solution in CH_2Cl_2, 2.3 mmol), and CH_2Cl_2 (15 mL) were used according to general procedure IX. The resulting residue was recrystallized from MeOH to afford **639** (0.046 g, 15%) as an orange solid: ^1H NMR (DMSO-d_6, 400 MHz) δ 10.39 (s, 1H), 8.20 (m, 3H), 7.45 (m, 2H), 6.90 (d, 1H).

Step C:

A mixture of **639** (0.045 g, 0.17 mmol), **482** (0.064 g, 0.18 mmol), potassium carbonate (0.047 g, 0.34 mmol) in 10 mL of acetone was heated to reflux. When the reaction was judged to be complete, the mixture was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The resulting solid was recrystallized

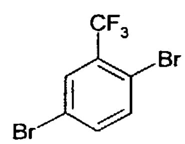
from CH_3CN, filtered and dried to provide **637** (19 mg, 23%) as a pale yellow solid: MS (ES) *m/z* 484 (M^+), 483 $(M-H)^-$; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.31 (s, 1H), 8.20 (m, 3H), 7.57 (m, 5H), 7.20 (m, 3H), 4.64 (s, 2H), 2.10 (s, 3H).

Example 260:



640

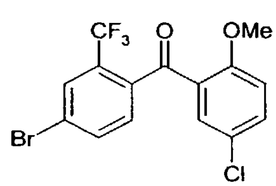
Step A:



641

To a round bottom flask equipped with a stir bar and nitrogen on demand were added copper (II) bromide (5.36 g, 0.024 mol) and CH_3CN (100 mL). The reaction mixture was cooled to 0 °C and t-butyl nitrite (3.8 mL, 3.3 g, 0.032 mol) was added dropwise over 15 min. 2-amino-5-bromobenzotrifluoride (5 g, 0.021 mol) was added dropwise over 15 min and the resulting mixture was allowed to continue stirring at 0 °C for 1.5 The mixture was then allowed to warm to RT and stir for an additional 16-18 h. When judged to be complete, the mixture was concentrated to ½ the original volume, was poured into 1N HCl and extracted with Et_2O. The organic layer was collected and concentrated under reduced pressure to afford **641** (5.5 g, 86 %) as a yellow oil: ^1H NMR (DMSO-d_6, 400 MHz) δ 7.96 (s, 1H), 7.78 (m, 2H).

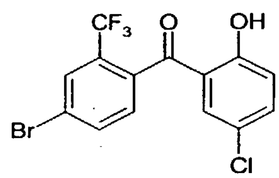
Step B:



642

A solution of **641** (5.5 g, 18 mmol) in 60 mL of ether was cooled to –78 °C in a dry ice/acetone bath. *n*-Butyllithium (9.2 mL of 2.5 M solution in hexanes, 23 mmol) was added dropwise over 10 min. The resulting mixture was stirred at –78 °C for an additional 10 min, then **183** (3.8 g, 18 mmol) was added in small portions over 10 min. The reaction mixture was allowed to warm to rt and continue stirring for 2 h and was poured into water and extracted with EtOAc. The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by flash chromatography using 2% EtOAc in hexanes as eluant to provide **642** (1.7 g, 24%) as a yellow oil: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.03 (d, 1H), 7.88 (m, 1H), 7.65 (dd, 1H), 7.60 (d, 1H), 7.36 (d, 1H), 7.16 (d, 1H), 3.47 (s, 3H).

Step C:



643

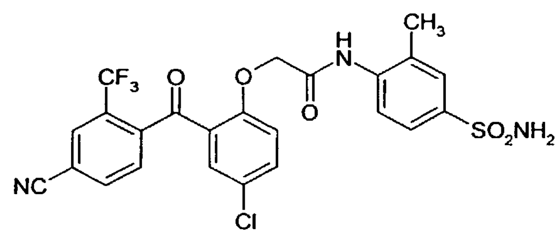
Anisole **642** (0.5 g, 1.27 mmol), BBr_3 (2.5 mL of a 1.0 M solution in CH_2Cl_2, 2.5 mmol), and CH_2Cl_2 (10 mL) were used according to general procedure IX to afford **643** (0.4 g, 83%) as a yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.71 (s, 1H), 8.03 (s, 1H), 7.92 (d, 1H), 7.50 (m, 3H), 6.90 (d, 1H).

Step D:

A mixture of **643** (0.400 g, 1.05 mmol), **470** (0.322 g, 1.05 mmol), potassium carbonate (0.290 g, 2.1 mmol) and sodium iodide (0.315 g, 2.1 mmol) in 15 mL of acetone was warmed to reflux and allowed to stir for 16 h. When the reaction was judged to be complete, the mixture was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The resulting residue was purified by flash chromatography using 3% MeOH/CH_2Cl_2 as eluant to provide a yellow solid. The solid was recrystallized from CH_3CN, filtered and dried to provide **640** (16 mg, 3%) as a white

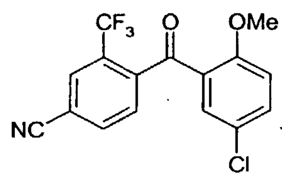
solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.31 (s, 1H), 8.01 (s, 1H), 7.90 (d, 2H), 7.66 (m, 5H), 7.47 (d, 1H), 7.24 (m, 3H), 4.67 (s, 2H), 2.23 (s, 3H).

Example 261:



644

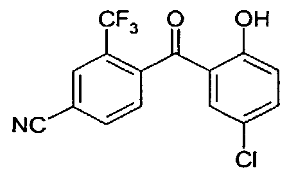
Step A:



645

Into a round bottom flask equipped with a stir bar, nitrogen on demand, and a reflux condenser were added **642** (0.250 g, 0.64 mmol), sodium cyanide (0.063 g, 1.3 mmol), copper (I) iodide (0.023 g, 0.12 mmol), and acetonitrile (10 mL). A stream of nitrogen was bubbled through the reaction mixture for 5 min., after which time tetrakis-(triphenylphosphine)palladium (0.086 g, 0.08 mmol) was added and the mixture was heated to reflux for 6 h. The reaction mixture was allowed to cool to rt and resulting precipitate was filtered. The precipitate was dissolved in EtOAc and washed with water. The organic layer was collected, filtered through a pad of celite, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide an orange residue. The residue was treated with Et_2O, filtered and dried to afford **645** (57 mg, 26%) as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.27 (s, 1H), 8.16 (d, 1H), 7.71 (dd, 1H), 7.64 (d, 1H), 7.56 (d, 1H), 7.22 (d, 1H), 3.54 (s, 3H).

Step B:



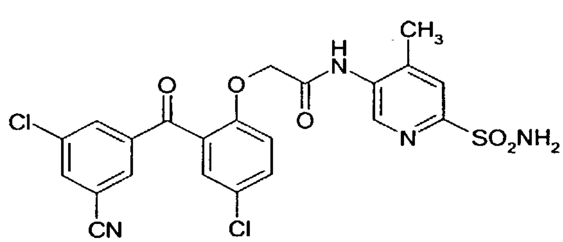
646

Anisole **645** (0.126 g, 0.37 mmol), BBr_3 (0.74 mL of a 1.0 M solution in CH_2Cl_2, 0.74 mmol), and CH_2Cl_2 (15 mL) were used according to general procedure IX. The resulting residue was treated with Et_2O and filtered to afford **646** (0.077 g, 64%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.80 (s, 1H), 8.25 (s, 1H), 8.16 (d, 1H), 7.64 (d, 1H), 7.55 (dd, 1H), 7.45 (d, 1H), 6.95 (d, 1H).

Step C:

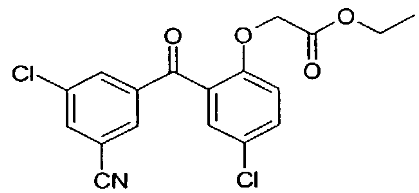
A mixture of **646** (0.077 g, 0.24 mmol), **482** (0.089 g, 0.25 mmol), potassium carbonate (0.066 g, 0.48 mmol) in 10 mL of acetone was heated to reflux. When the reaction was judged to be complete, it was allowed to cool to rt and was poured into EtOAc and water. The organic layer was collected, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The resulting residue was treated with Et_2O to provide a yellow solid. The solid was recrystallized from CH_3CN, filtered and dried to provide **644** (11 mg, 3%) as a pale yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.31 (s, 1H), 8.18 (s, 1H), 8.05 (d, 1H), 7.64 (m, 6H), 7.23 (m, 3H), 4.69 (s, 2H), 2.17 (s, 3H).

Example 262:



647

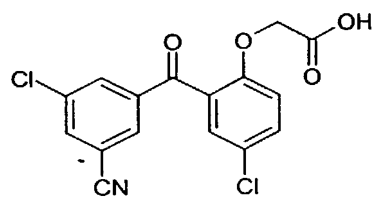
Step A:



648

Phenol **477** (0.345 g, 1.2 mmol), K_2CO_3 (0.326 g, 2.4 mmol), ethyl bromoacetate (0.14 mL, 0.207 g, 1.3 mmol) and acetone (10 mL) were used according to general procedure II to provide **648** as an orange oil (0.46 g, >99%). The product was without further purification:. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.28 (t, 1H), 8.04 (d, 1H), 7.98 (t, 1H), 7.58 (dd, 1H), 7.47 (d, 1H), 7.11(d, 1H), 4.73 (s, 2H), 4.07 (m, 2H), 1.11 (m, 3H).

Step B:



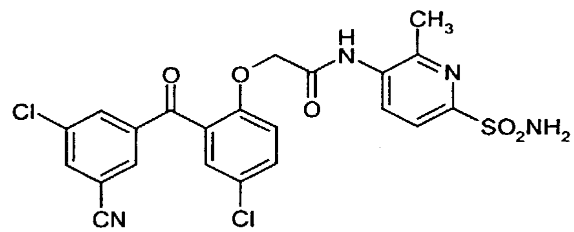
649

Ester **648** (0.46 g, 1.2 mmol), THF (4 mL), water (1 mL), EtOH (1 mL) and LiOH (0.128 g, 3.1 mmol) were used according to general procedure III to afford **649** (0.25 g, 60 %) as a yellow foam. The product was used without further purification: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.1 (bs, 1H), 8.27 (s, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.57 (dd, 1H), 7.45 (d, 1H), 7.08 (d, 1H), 4.63 (s, 2H), 4.07 (m, 2H), 1.11 (m, 3H).

Step C:

Acid **649** (0.120 g, 0.34 mmol), oxalyl chloride (0.04 mL, 0.06 g, 0.48 mmol), N, N-dimethylformamide (1 drop), and CH_2Cl_2 (7 mL) were used according to general procedure V. The resulting acid chloride, aniline **490** (0.064 g, 0.34 mmol), $NaHCO_3$ (0.14 g, 1.7 mmol), acetone (7 mL), and water (1 mL) were used according to general procedure VI. The resulting residue purified by flash chromatography using 3% MeOH: CH_2Cl_2 as eluant to afford **647** (0.01 g, 6 %) as a pale yellow solid: MS (ES+) *m/z* 519 (M^+): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.66 (s, 1H), 8.26 (s, 1H), 8.12 (s, 1H), 8.04 (s, 1H), 7.75 (d, 1H), 7.62 (dd, 1H), 7.50 (d, 1H), 7.34 (s, 2H), 7.20 (d, 1H), 4.81 (s, 2H), 2.20 (s, 3H) ppm.

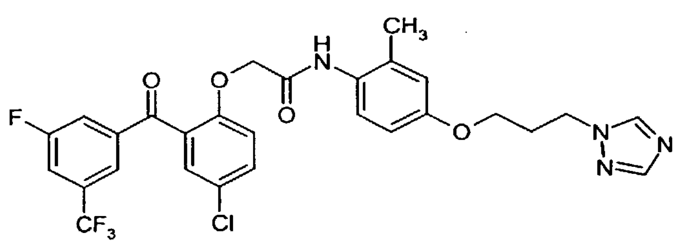
Example 263:



650

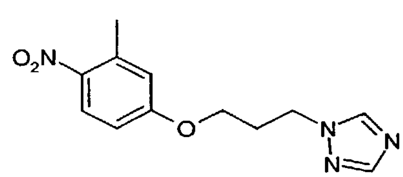
Acid **649** (0.1g, 0.3 mmol) was converted to the acid chloride by general procedure V, and coupled with 5-amino-6-methyl-2-pyridinesulfonamide (0.06g, 0.33 mmol, 1.1 eq.) as outlined in Step E for the synthesis of compound **503** in example 206 to give **650**. LCMS (ES $^+$) 520 m+1/z. ^{1}H NMR (DMSO-d_6) δ 9.65 (br s, 1H, NH), 8.3(s, 1H, Ar), 8.1 (m, 2H, Ar), 8.0 (s, 1H, Ar), 7.7 (d, 1H, Ar), 7.6 (dd,1H, Ar), 7.5 (d, 1H, Ar), 7.32 (bs, 2H, NH_2), 7.2 (d,1H, Ar), 4.8 (s, 2H, CH_2), 2.3 (s, 3H, CH_3).

Example 264:



651

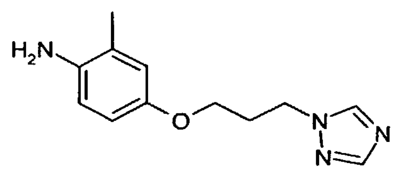
Step A:



652

4-(3-Bromo-propoxy)-2-methyl-1-nitrobenzene (1 g, 3.6 mmol) and 1,2,4-triazole (Aldrich, 0.25 g, 3.6 mmol) were used in the same manner as to prepare compound 139. Compound **652** (0.45 g, 48%) was obtained as an oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.4 (br s, 4H), 2.45 (s, 3H), 4.1 (t, 2H), 6.9 (dd, 1H), 6.92 (d, 1H), 7.9 (d, 2H), 8 (d, 1H).

Step B:



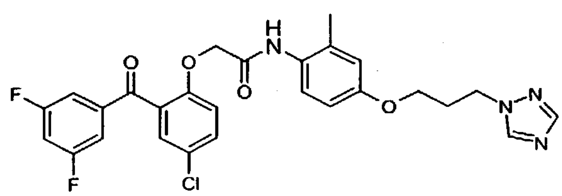
653

Compound **652** was used in the same manner as that to prepare compound 140. Aniline **653** was obtained as an oil (0.33 g, 84%). The compound was used without further purification.

Step C:

Acid 71 (0.26 g, 0.7 mmol), oxalyl chloride (0.09 mL, 1 mmol), DMF (1 drop), and CH_2Cl_2 were used according to general procedure V to afford the desired acid chloride. The acid chloride, aniline 653 (0.16 g, 0.7 mmol), $NaHCO_3$ (0.3 g, 3 mmol), acetone (8 mL), and water (0.3 mL) were used according to general procedure VI. Flash column chromatography of the crude product on silica gel with 2% methanol in CH_2Cl_2 afforded 651 (0.05 g, 12%) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.9 (s, 3H), 2.1-2.2 (m, 2H), 3.8 (t, 2H), 4.3 (t, 2H), 4.66 (s, 2H), 6.6 (dd, 1H), 6.7 (d, 1H), 7.03 (d, 1H), 7.2 (d, 1H), 7.5 (d, 1H), 7.6 (dd, 1H), 7.8-7.82 (m, 2H), 7.9 (s, 1H), 8 (d, 1H), 8.5 (s, 1H), 9.02 (s, 1H).

Example 265:

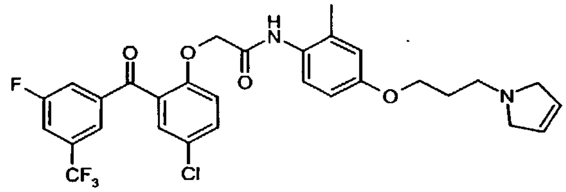


654

Acid **49** (0.14 g, 0.4 mmol), oxalyl chloride (0.2 mL, 2 mmol), DMF (1 drop), and CH_2Cl_2 were used according to general procedure V. The resulting acid chloride, aniline **653** (0.1 g, 0.4 mmol), $NaHCO_3$ (0.17 g, 1.7 mmol), acetone (5 mL), and water (0.1 mL) were used according to general procedure VI. Flash column chromatography of the crude product on silica gel with 2% methanol in CH_2Cl_2 resulted in **654** (0.04 g, 18%) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.9 (s, 3H), 2.1-2.2 (m, 2H), 3.8 (t, 2H), 4.3 (t, 2H), 4.7 (s,

2H), 6.6 (dd, 1H), 6.7 (d, 1H), 7.08 (d, 1H), 7.2 (d, 1H), 7.3-7.4 (m, 2H), 7.42-7.6 (m, 3H), 7.9 (s, 1H), 8.5 (s, 1H), 9 (s, 1H).

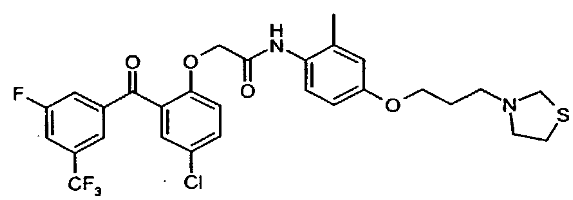
Example 266:



655

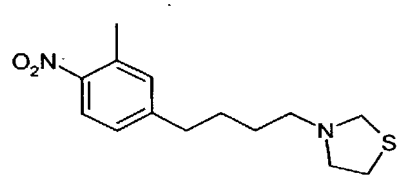
Acid **71** (1.4 g, 3.6 mmol), thionyl chloride (1.3 mL, 18 mmol), DMF (1 drop), and CH_2Cl_2 were used according to general procedure V to afford the desired acid chloride. The acid chloride, aniline **595** (0.84 g, 3.6 mmol), $NaHCO_3$ (1.36 g, 16 mmol), acetone (50 mL), and water (1 mL) were used according to general procedure VI. Flash column chromatography of the crude product on silica gel with 5% methanol in CH_2Cl_2 afforded **655** (0.53 g, 25%) as a solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.7-1.8 (m, 2H), 1.95 (s, 3H), 2.6-2.7 (m, 2H), 3.4 (br s, 4H), 3.9 (t, 2H), 4.66 (s, 2H), 5.7 (s, 2H), 6.6 (dd, 1H), 6.7 (d, 1H), 7.0 (d, 1H), 7.2 (d, 1H), 7.5 (d, 1H), 7.6 (dd, 1H), 7.8-7.82 (m, 2H), 8 (d, 1H), 9.02 (s, 1H).

Example 267:



656

Step A:



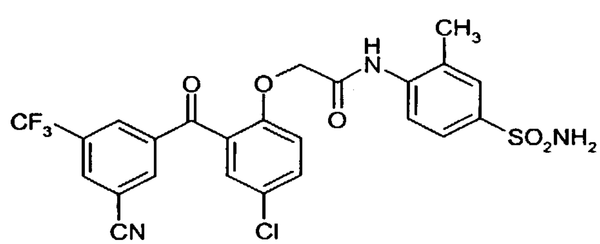
657

4-(3-Bromo-propoxy)-2-methyl-1-nitrobenzene (1 g, 3.6 mmol) and thiazolidine (Aldrich, 0.34 mL, 4.3 mmol) were used in the same manner as to prepare compound **139**. Compound **657** (0.45 g, 48%) was obtained as an oil and was used without further purification.

Step B:

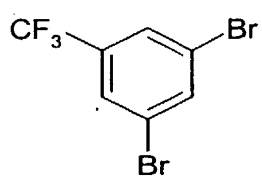
The nitro group of **657** (1 g, 3.5 mmol) was reduced under catalytic conditions (H_2, 10% Pd/C in EtOH). Acid **71** (1.3 g, 3.5 mmol), thionyl chloride (1.3 mL, 18 mmol), DMF (1 drop), and CH_2Cl_2 were used according to general procedure V to afford the desired acid chloride. The resultant crude aniline, acid chloride, $NaHCO_3$ (1.4 g, 16 mmol), acetone (50 mL), and water (1 mL) were used according to general procedure VI. Flash column chromatography of the crude product on silica gel with EtOAc:hexane (7:3) resulted in 656 (0.14 g, 7%) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.8 (m, 2H), 2 (s, 3H), 2.4 (t, 2H), 2.8 (t, 2H), 3 (t, 2H), 3.9-4 (m, 5H), 4.7 (s, 1H), 6.6 (dd, 1H), 6.7 (d, 1H), 7.0 (d, 1H), 7.2 (d, 1H), 7.5 (d, 1H), 7.6 (dd, 1H), 7.8-7.82 (m, 2H), 8 (d, 1H), 9.02 (s, 1H).

Example 268:



658

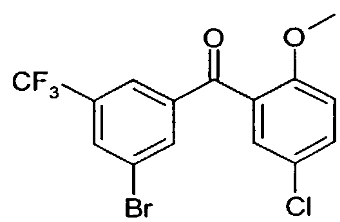
Step A:



659

To a solution of copper (II) bromide (5.36 g, 24 mmol) in acetonitrile (100 ml) at 0 °C was added t-butyl nitrite (3.8 ml, 32 mmol) dropwise, and then 3-amino-5-bromobenzotrifluoride (5 g, 21 mmol) dropwise. The mixture was stirred at 0 °C for 1.5 h, then at room temperature for 16 h. The mixture was then concentrated to half of its original volume in vacuo, and then poured into 1N HCl (120 ml). This mixture was extracted with ether (100 mL). The organic layer was washed with 1N HCl, dried (Na_2SO_4), filtered, concentrated in vacuo (Note: product is fairly volatile, and should not be exposed to high vacuum for extended periods of time) to give **659** as a brown oil (5.12 g), which was used as is without further purification. ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.82 (s, 1H), 7.67 (s, 2H).

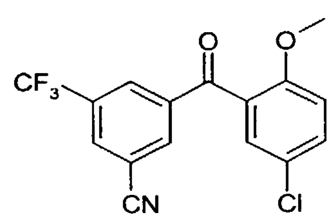
Section B:



660

659 (5.12 g), *N*-methyl-*N*-methoxy-2-methoxy-5-chlorobenzamide (3.6 g, 16.8 mmol), and n-butyllithium (8.76 ml of 2.7M solution in heptane) were treated according to the procedure outlined in Part A of Example 2 to give **660** (3.36 g), which was used as is without further purification. ^{1}H NMR ($CDCl_3$, 400MHz) δ 8.02 (s, 1H), 7.89 (d, 2H), 7.46 (dd, 1H), 7.38 (d, 1H), 6.92 (d, 1H), 3.66 (s, 3H).

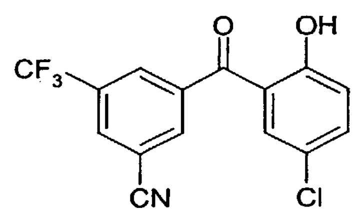
Section C:



661

660 (3.36 g, 8.55 mmol), sodium cyanide (838 mg, 17 mmol), copper (I) iodide (325 mg, 1.7 mmol), and tetrakis(triphenylphospine)palladium (0) (987 mg, 0.86 mmol) were used according to General Procedure A to give **661** (1.35 g) after silica gel purification (10% ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 400MHz) δ 8.19 (s, 1H), 8.13 (s, 1H), 8.04 (s,1H), 7.50 (dd, 1H), 7.43 (d, 1H), 6.94 (1H), 3.65 (s, 3H).

Section D:



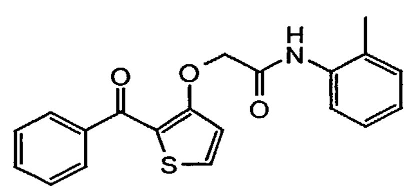
662

661 (1.35 g, 3.98 mmol) was treated according to the procedure for the synthesis of compound **4** to give **662** (1.29 g, >99%) as a yellow oil, which was used without further purification. ^{1}H NMR ($CDCl_3$, 300MHz) δ 11.49 (s, 1H), 8.20-8.16 (m, 3H), 7.59 (dd, 1H), 7.38 (d, 1H), 7.15 (d, 1H).

Step E:

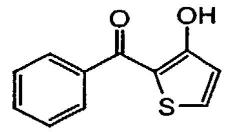
662 (487 mg, 1.5 mmol) and **470** were treated according to **Step D** in **Example 197** to give a crude product which was purified by silica gel chromatography (8:1:1 CH_2Cl_2/ethyl acetate/methanol) and triturated with ether to give **658** (315 mg) as an off-white solid. ^{1}H NMR (DMSO-d$_6$, 400MHz) δ 9.41 (s, 1H), 8.56 (s, 1H), 8.45 (s, 1H), 8.27 (s, 1H), 7.66-7.52 (m, 5H), 7.19 (m, 3H), 4.76 (s, 2H), 2.12 (s, 3H); MS(ES-): *m/z* 550 $(M-H)^-$.

Example 269:



663

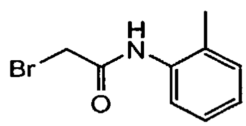
Step A:



664

A mixture of 3-methoxythiophene (1.14 g, 10 mmol), aluminum chloride (2.67 g, 20 mmol), and benzoyl chloride (1.16 mL, 10 mmol) in 50 mL of methylene chloride was heated to reflux for 20 h. The reaction mixture was then poured over ice and stirred at room temperature for 5 h, after which the aqueous layer was separated and extracted with 20 mL of CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1.897 g of orange oil. Purification by flash chromatography using 5-7% EtOAc/hexane as eluant gave **664** (0.823 g, 40%) as a yellow crystalline solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.35 (s, 1 H), 7.92 (dd, 2 H), 7.56-7.46 (m, 4 H), 6.83 (d, 1 H).

Step B:



665

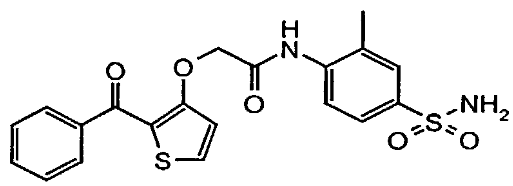
A solution of *o*-toluidine (2.67 mL, 25 mol) and pyridine (2.2 mL, 27.5 mmol) in 200 mL of chloroform was cooled to 0 °C in an ice bath. Bromoacetyl bromide (2.4 mL, 27.5 mmol) was added dropwise over 7 min, and the resulting mixture was allowed to slowly warm to rt and stirred for 24 h. The reaction mixture was then poured into 150 mL of water. The aqueous layer was separated and extracted with 100 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **665** (5.86 g, quantitative): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (br s, 1 H), 7.81 (d, 1H), 7.20-7.17 (m, 2 H), 7.10-7.06 (m, 1 H), 4.04 (s, 2 H), 2.27 (s, 3 H).

Step C:

A mixture of **664** (0.204 g, 1.0 mmol), **665** (0.235 g, 1.03 mmol), and potassium carbonate (0.622 g, 4.5 mmol) in 10 mL of acetone was warmed to reflux for 6 h, then stirred at room temperature an additional 16 h. The reaction mixture was then poured into 30 mL of

water and extracted with two 30-mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 0.448 g of crude material. Purification by flash chromatography using 35% EtOAc/hexanes as the eluant gave **663** (0.272 g, 77%): MS (ES+) *m/z* 352 (M+H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (br s, 1 H), 7.81-7.79 (m, 2 H), 7.59 (d, 1 H), 7.42-7.38 (m, 3 H), 7.19-7.16 (m, 2 H), 7.10-7.07 (m, 1 H), 6.93 (d, 1 H), 4.73 (s, 2 H), 2.19 (s, 3 H).

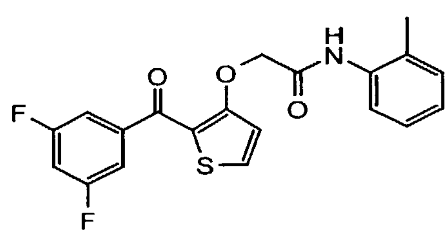
Example 270:



666

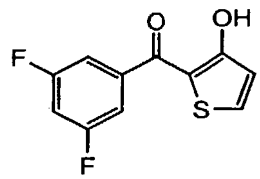
A mixture of **664** (0.218 g, 1.07 mmol), **470** (0.338 g, 1.1 mmol), and potassium carbonate (0.622 g, 4.5 mmol) in 10 mL of acetone was warmed to reflux for 5 h. The reaction mixture was then poured into 30 mL of water and extracted with 30 mL of EtOAc. The pH of the aqueous layer was adjusted to 7 using 3 M HCl, then extracted with 30 mL of EtOAc. The combined organic layers were filtered to remove yellow solid, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.360 g of crude material. This material was suspended in CH_2Cl_2 and acetone and filtered, then suspended in MeOH and filtered to give **666** (0.076 g, 17%): MS (ES+) *m/z* 431 (M+H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.29 (s, 1 H), 7.96 (d, 1 H), 7.77 (d, 2 H), 7.67 (d, 1 H), 7.62 (d, 1 H), 7.58 (dd, 1 H), 7.50 (t, 1 H), 7.43-7.48 (m, 2 H), 7.23 (br s, 2 H), 7.15 (d, 1 H), 4.83 (s, 2 H), 2.16 (s, 3 H).

Example 271:



667

Step A:



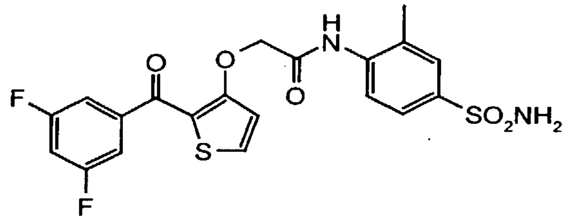
668

A mixture of 3-methoxythiophene (1.14 g, 10 mmol), aluminum chloride (2.70 g, 20.2 mmol), and 3,5-difluorobenzoyl chloride (1.18 mL, 10 mmol) in 50 mL of methylene chloride was heated to reflux for 20 h, then stirred at room temperature for 27 h. The reaction mixture was then poured over ice and stirred at room temperature for 40 min, after which the aqueous layer was separated and extracted with 20 mL of CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1.214 g of brown solid. Purification by flash chromatography using 2% EtOAc/hexane as eluant gave **668** (0.518 g, 22%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.04 (s, 1 H), 7.57 (d, 1 H), 7.43 (dd, 2 H), 7.02-6.97 (m, 1 H), 6.84 (d, 1 H).

Step B:

A mixture of **668** (0.192 g, 0.80 mmol), **665** (0.188 g, 0.82 mmol), and potassium carbonate (0.498 g, 3.6 mmol) in 10 mL of acetone was warmed to reflux for 6 h. The reaction mixture was then poured into 30 mL of water and extracted with two 30-mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give crude material. Purification by flash chromatography using 35-40% EtOAc/hexane as eluant gave **667** as a yellow solid (0.069 g, 22%): MS (ES+) *m/z* 388 (M+H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (br s, 1 H), 7.74 (d, 1 H), 7.66 (d, 1 H), 7.36-7.32 (m, 2 H), 7.23-7.21 (m, 2 H), 7.15-7.10 (m, 1 H), 6.99 (d, 1 H), 6.96-6.89 (m, 1 H), 4.80 (s, 2 H), 2.32 (s, 3 H).

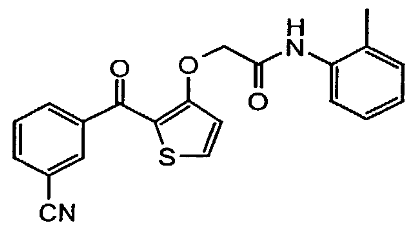
Example 272:



669

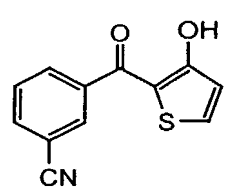
A mixture of **668**(0.192 g, 0.80 mmol), **470** (0.252 g, 0.82 mmol), and potassium carbonate (0.498 g, 3.6 mmol) in 10 mL of acetone was warmed to reflux for 6 h. The reaction mixture was then poured into 30 mL of water and extracted with two 30-mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.272 g of crude material. Purification by flash chromatography using 35-50% EtOAc/hexane as eluant gave **669** as a yellow solid (0.103 g, 28%): MS (ES+) *m/z* 467 (M+H); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.47 (br s, 1 H), 8.06 (d, 1 H), 7.72-7.52 (m, 3 H), 7.50-7.40 (m, 3 H), 7.26 (br s, 2 H), 7.17 (d, 1 H), 4.89 (s, 2 H), 2.23 (s, 3 H).

Example 273:



670

Step A:



671

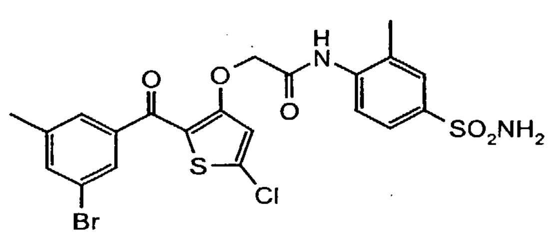
A mixture of 3-methoxythiophene (1.14 g, 10 mmol), aluminum chloride (2.78 g, 20.8 mmol), and **284** (10 mmol) in 50 mL of methylene chloride was heated to reflux for 24 h, then stirred at room temperature for 15 h. The reaction mixture was then poured over ice

and stirred at room temperature for 1 h, after which the aqueous layer was separated and extracted with 35 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 2.239 g of brown oil. Purification by flash chromatography using 5% EtOAc/hexane as eluant gave **671** (0.195 g, 9%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.04 (s, 1 H), 8.19 (s, 1 H), 8.13 (d, 1 H), 7.83 (d, 1 H), 7.64-7.58 (m, 2 H), 6.86 (d, 1 H).

Step B:

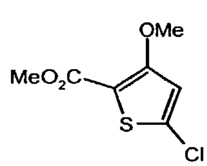
A mixture of **671** (0.164 g, 0.72 mmol), **665** (0.168 g, 0.74 mmol), and potassium carbonate (0.448 g, 3.24 mmol) in 12 mL of acetone was warmed to reflux for 15 h, then stirred at room temperature for an additional 5.5 h. Since the reaction mixture went dry overnight, another 10 mL of acetone was added, and the mixture was heated to reflux for 6 h, then stirred at room temperature overnight. The reaction mixture was poured into 50 mL of water and extracted with two 35-mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 1.251 g of brown oil. Purification by flash chromatography using 30-40% EtOAc/hexane as eluant gave **670** as a yellow solid (0.033g, 12%): MS (ES+) *m/z* 377 (M+H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63 (br s, 1 H), 8.07 (s, 1 H), 8.01 (d, 1 H), 7.73-7.68 (m, 2 H), 7.65 (d, 1 H), 7.55 (t, 1 H), 7.20-7.18 (m, 2 H), 7.09 (t, 1 H), 6.97 (d, 1 H), 4.76 (s, 2 H), 2.27 (s, 3 H).

Example 274:



672

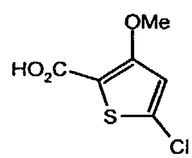
Step A:



673

(Reference: *Synthesis*, **1984**, 847). Sulfury chloride (2 mL, 25.5 mmol) was added to a stirred mixture of methyl 3-methoxy-2-thiophenecarboxylate (Avocado, 4 g, 23.2 mmol) in $CHCl_3$ (40 mL). The reaction mixture was gently stirred for 4-6 h after which it was concentrated. The concentrate was dissolved in glacial AcOH and HCl gas was bubbled in. The resultant mixture was left standing for 48 h. Following solvent extraction and flash column chromatography on silica with CH_2Cl_2, **673** (2.8 g, 58%) was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.7 (s, 3H), 3.9 (s, 3H), 7.3 (s, 1H).

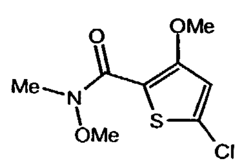
Step B:



674

673 (1 g, 4.8 mmol), lithium hydroxide dihydrate (1 g), EtOH (10 mL), and water (10 mL) were used according to general procedure III. Following work-up, **674** (0.59 g, 64%) was obtained as a light brown solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.9 (s, 3H), 7.2 (s, 1H), 12.6 (br s, 1H).

Step C:

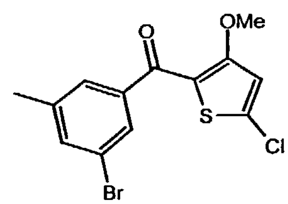


675

To a solution of **674** (0.59 g, 3.1 mmol) in THF (10 mL) was added carbonyl diimidazole (0.5 g, 3.1 mmol), N,O-dimethylhydroxylamine hydrochloride (0.45 g, 4.65 mmol), and a catalytic amount of N,N-dimethylaminopyridine. The reaction mixture was stirred at room temperature under argon for 24 h. The mixture was then diluted with EtOAc, and this was washed with water. After drying ($MgSO_4$) and solvent removal, the crude product was purified by flash column chromatography on silica gel with 5% MeOH in

CH_2Cl_2 to give **675** (0.36 g, 49%) as an off-white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.1 (s, 3H), 3.7 (s, 3H), 3.9 (s, 3H), 7.2 (s, 1H).

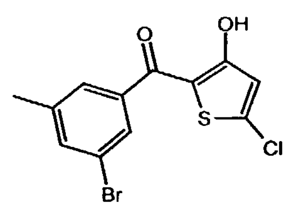
Step D:



676

675 (0.36 g, 1.5 mmol), 3,5-dibromotoluene (Avocado, 0.34 g, 1.4 mmol), and n-butyllithium (1.1 mL, 1.5 mmol of 1.4 M hexane solution) in ether were used according to general procedure VIII. Following work-up and flash column chromatography on silica with CH_2Cl_2, **676** (0.3 g, 58%) was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.3 (s, 3H), 3.8 (s, 3H), 7.4 (s, 1H), 7.5 (s, 1H), 7.6 (s, 1H), 7.62 (s, 1H).

Step E:



677

676 (0.3 g, 0.9 mmol), boron tribromide (1.7 mL, 1.7 mmol), and CH_2Cl_2 (10 mL) were used according to general procedure IX. **677** (0.26 g, 87%) was obtained as a solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.3 (s, 3H), 6.8 (s, 1H), 7.46 (s, 1H), 7.6 (s, 1H), 7.62 (s, 1H), 11.6 (s, 1H).

Step F:

A mixture of **677** (0.26 g, 0.8 mmol), **470** (0.24 g, 0.8 mmol) and potassium carbonate (0.6 g, 4 mmol) in DMF (10 mL) was stirred for 12 h. Water was added to the reaction mixture, which was in turn extracted with EtOAc. The EtOAc extract was further washed with water, brine and dried ($MgSO_4$). After solvent removal, the crude product was

subjected to flash column chromatography on silica gel with 5% MeOH in CH_2Cl_2 to give an impure **672**, which was recrystallized from EtOAc. **672** (0.016 g, 4%) was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.2 (s, 3H), 2.3 (s, 3H), 4.9 (s, 2H), 7.2 (s, 1H), 7.4 (s, 1H), 7.5-7.8 (m, 7H), 9.4 (s, 1H).

Example 275

Inhibition of Viral Replication

I. HeLa Cell Assay

The HeLa cell assay was performed according to a modifcation of Kimpton J. and Emerman M., Detection of replication-competent and pseudotyped human immunodeficiency virus with a sensitive cell line on the basis of activation of an integrated β-galactosidase gene, *J. Virol.* 66:2232-2239 (1992), in which HIV-1 infection is detected by the activation of an HIV-LTR driven β-galactosidase reporter that is integrated into the genome of a $CD4^+$ HeLa cell line. Quantitation of β-galactosidase is achieved by measuring the activation of a chemiluminescent substrate (Tropix). The concentration of each compound required to inhibit 50% (IC_{50}) of the HIV-1 induced β-galactosidase signal, relative to untreated controls, was determined for each isogenic, recombinant virus.

A. Experimental Procedure

Growth and Maintenance of the CD4-HIV LTR-β-gal HeLa cell line.

HeLa-CD4-LTR-β-gal cells were obtained from the NIH AIDS Research and Reference Reagent Program. Cells were propagated in DMEM containing 10% fetal bovine serum, 0.2 mg/ml geneticin and 0.1 mg/ml hygromycin B. Cells were routinely split by trypsinization when confluency reached 80% (approximately every 2 to 3 days).

B. Construction of HIV-1 reverse transcriptase (RT) mutants

DNA encoding the HIV-1 reverse transcriptase was subcloned from a M13 phage into a general shuttle vector, pBCSK+, as a ~1.65 kbp EcoRI/HindIII ended DNA fragment. The HIV DNA insert of the resulting plasmid, pRT2, was completely sequenced on both strands prior to use in site directed mutagenesis experiments. Specific amino acid

replacements were made using Stratagene Quick Change reagents and mutagenic oligonucleotides from Oligos. Following mutagenesis, the entire mutant RT coding sequence was verified by sequencing both DNA strands.

C. Construction of isogenic HIV-1 RT mutant virus

Mutant HIV-1 strains were isolated by a modified Recombinant Virus Assay (Kellam P. and Larder B., Recombinant virus assay: a rapid, phenotypic assay for assessment of drug susceptibility of human immunodeficiency virus type 1 isolates, *Antimicrobial Agents and Chemotherapy*, 38:23-30, 1994). 1 X 10^7 Jurkat T-cells (maintained in RPMI containing 10% fetal bovine serum, split 1:5 every 5 to 6 days) were co-transfected with EcoRI/HindIII digested mutant RT plasmid and Bst EII-digested HIV-$1_{HXB2\Delta RT}$ DNA in the presence of DMRIE-C transfection reagent (Gibco) according to supplier's recommended protocol. Each mutant RT coding sequence was crossed into the RT-deleted HIV-1 viral DNA backbone by in vivo homologous recombination. Transfected cell cultures were expanded and monitored until syncitia formation and CPE were extensive. Virus was harvested by clear spin of the culture supernatants and frozen at - 80 C as primary stock. Recombinant progeny virus was sequenced in the RT region to confirm the mutant genotype. Virus stocks were further expanded by infection of Jurkat cells, harvested and stored as frozen aliquots. Stocks were titered in HeLa MAGI cells for assay.

D. Titering of virus stocks

The HIV-1_{HXB2} mutants were titered in the HeLa MAGI assay system to determine the relative light units (RLU) per ml, a measure of infectivity relevant for this assay system. Virus stocks were diluted in a 2-fold series into DMEM containing 10% fetal bovine serum plus 20ug/ml DEAE-dextran and assayed as described in the Experimental Protocol section, below.

E. Experimental Protocol

96-well microtiter plate(s) (Costar #3598) were seeded with 3 X 10^3 HeLa-CD4-LTR-β- gal in 100μl DMEM containing 10% fetal bovine serum. Plates were placed in a 37 ^{0}C, 5% CO_2 humidified incubator overnight. The following day, mutant virus stocks were

thawed in a room temperature water bath and diluted into DMEM containing 10% fetal bovine serum and 20μg/ml DEAE-dextran to achieve an input of 1500 to 2000 RLU/ml. All media was removed with an 8 channel manifold aspirator and 35μl (50 to 70 total RLUs) of diluted virus was added to each well for virus adsorption. Plates were placed in a 37 ^{0}C, 5% CO_2 humidified incubator for 1.5 to 2 hours.

Compound titration plates were prepared at 1.35X final concentration during the virus adsorption period. Compounds were titrated robotically in a five-fold stepwise manner from 2.7 μM (2μM final) to 1.35 pM (1pM final). This scheme allows 8 compounds to be tested per 96-well plate with 10 dilution points and 2 controls per compound (n=1). Compounds were titrated into DMEM containing 10% fetal bovine serum plus 0.135% DMSO (0.1% final). 100μl of titrated compound was removed from every well of the titration plate and added to the virus adsorption plate. Plates were placed in a 37 ^{0}C, 5% CO_2 humidified incubator.for 72 hours.

Following incubation, supernatants were aspirated from every well as described above and 100μl of phosphate buffered saline was added. The PBS was then aspirated as above and 15μl of lysis buffer (Tropix) was added. Plates were maintained at room temperature for 10 minutes during which time the chemiluminescent substrate (Tropix) was diluted 1:50 into room temperature substrate dilution buffer (Tropix). 100μl of diluted substrate was then added to each well. Plates were incubated at room temperature for 1 to 1.5 hours. Following incubation, the chemiluminescence of each well was measured with a Dynatech plate reader using the following settings:

PARAMETER	VALUE
run	cycle
data	all
gain	low
cycles	1s
pause	2s
rows	abcdefgh
temp	room
stir	off

The output raw data, RLUs, were analyzed by nonlinear regression to determine IC_{50} values (see data analysis section below).

F. Data Analysis

Relative light units (RLU) are expressed as % control:

(RLU at compound [ ] / RLU no compound)*100 = % Control

The concentration of compound that inhibits 50% of the signal produced in untreated samples (IC_{50}) is determined by the following nonlinear regression model available on the ROBOSAGE software package:

$$Y = V_{max}*(1-(X^n/(K^n + X^n)))$$

This equation describes a sigmoidal inhibition curve with a zero baseline. X is inhibitor concentration and Y is the response being inhibited. V_{max} is the limiting response as X approaches zero. As X increases without bound, Y tends toward its lower limit, zero. K is the IC_{50} for the inhibition curve, that is, Y is equal to 50% of V_{max} when X = K.

Results in Table 1 are reported as ranges of representative IC_{50} values.

II. MT4 Cell Assay

A. Experimental Procedure

Antiviral HIV activity and compound-induced cytotoxicity were measured in parallel by means of a propidium iodide based procedure in the human T-cell lymphotropic virus transformed cell line MT4. Aliquots of the test compounds were serially diluted in medium (RPMI 1640, 10% fetal calf serum (FCS), and gentamycin) in 96-well plates (Costar 3598) using a Cetus Pro/Pette. Exponentially growing MT4 cells were harvested and centrifuged at 1000 rpm for 10 min in a Jouan centrifuge (model CR 4 12). Cell pellets were resuspended in fresh medium (RPMI 1640, 20% FCS, 20% IL-2, and gentamycin) to a density of 5 x 105 cells/ml. Cell aliquots were infected by the addition of HIV-1 (strain IIIB) diluted to give a viral multiplicity of infection of 100 x TCID50. A similar cell aliquot was diluted with medium to provide a mock-infected control. Cell infection was allowed to proceed for 1 hr at 37°C in a tissue culture incubator with humidified 5% CO_2 atmosphere. After the 1 hr incubation the virus/cell suspensions were diluted 6-fold with fresh medium, and 125 µl of the cell suspension was added to each

well of the plate containing pre-diluted compound. Plates were then placed in a tissue culture incubator with humidified 5% CO_2 for 5 days. At the end of the incubation period, 27 µl of 5% Nonidet-40 was added to each well of the incubation plate. After thorough mixing with a Costar multitip pipetter, 60 µl of the mixture was transferred to filter-bottomed 96-well plates. The plates were analyzed in an automated assay instrument (Screen Machine, Idexx Laboratories). The control and standard used was 3'-azido-3'-deoxythymidine tested over a concentration range of 0.01 to 1 µM in every assay. The expected range of IC_{50} values for 3'-azido-3'-deoxythymidine is 0.04 to 0.12 µM. The assay makes use of a propidium iodide dye to estimate the DNA content of each well.

B. Analysis

The antiviral effect of a test compound is reported as an IC_{50}, i.e. the inhibitory concentration that would produce a 50% decrease in the HIV-induced cytopathic effect. This effect is measured by the amount of test compound required to restore 50% of the cell growth of HIV-infected MT4 cells, compared to uninfected MT4 cell controls. IC_{50} was calculated by RoboSage, Automated Curve Fitting Program, version 5.00, 10-Jul-1995.

For each assay plate, the results (relative fluorescence units, rfU) of wells containing uninfected cells or infected cells with no compound were averaged, respectively. For measurements of compound-induced cytotoxicty, results from wells containing various compound concentrations and uninfected cells were compared to the average of uninfected cells without compound treatment. Percent of cells remaining is determined by the following formula:

Percent of cells remaining = (compound-treated uninfected cells, rfU / untreated uninfected cells) x 100.

A level of percent of cells remaining of 79% or less indicates a significant level of direct compound-induced cytotoxicity for the compound at that concentration. When this condition occurs the results from the compound-treated infected wells at this concentration are not included in the calculation of IC_{50}.

For measurements of compound antiviral activity, results from wells containing various compound concentrations and infected cells are compared to the average of uninfected and infected cells without compound treatment. Percent inhibition of virus is determined by the following formula:

Percent inhibition of virus = (1-((ave. untreated uninfected cells - treated infected cells) / (ave. untreated uninfected cells - ave. untreated infected cells)))x 100

References:

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2. Schwartz, O., et al,. A rapid and simple colorimetric test for the study of anti-HIV agents, *AIDS Res. and Human Retroviruses* 4 (6): 441-447, 1988..

3. Daluge, S.M., et al., 5-chloro-2'3'-deoxy-3'fluorouridine (935U83), a selective anti-human immunodeficiency virus agent with an improved metabolic and toxicological profile. *Antimicro. Agents and Chemother*. 38 (7): 1590-1603, 1994.

4. Dornsife, R.E., et al., Anti-human immunodeficiency virus synergism by zidovudine (3'-azidothymidine) and didanosine (dideoxyinosine) contrasts with the additive inhibition of normal human marrow progenitor cells, *Antimicro. Agents and Chemother*. 35 (2): 322-328, 1991.

Results in Table 1. are expressed as representative IC_{50} ranges.

Table 1

Compound Number	Virus Type	IC50 (nM) Range *	Assay
1	HIV-1	C	MT4
	NEV-R	D	MT4
5	HIV-1	B	MT4
	NEV-R	C	MT4
8	HIV-1	B	MT4
	NEV-R	C	MT4
9	HIV-1	B	MT4
	NEV-R	C	MT4
62	HIV-1	A	MT4
	HIV-2	D	MT4
	NEV-R	A	MT4
	E138K	A	HeLa
	G190A	A	HeLa
	G190E	A	HeLa
	K101E	A	HeLa
	K103N	A	HeLa
	K103N/G190A	B	HeLa
	K103N/L1001	A	HeLa

	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	B	HeLa
	L1001	A	HeLa
	P225H	A	HeLa
	P236L	B	HeLa
	V106A	B	HeLa
	V106A/Y181C	B	HeLa
	V1061	A	HeLa
	V1061/Y181C	B	HeLa
	V1081	A	HeLa
	V1081/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
	Y188C	A	HeLa
78	HIV-1	A	
	NEV-R	A	
	E138K	A	HeLa
	G190A	A	HeLa
	G190E	A	HeLa
	K101E	A	HeLa
	K103N	A	HeLa
	K103N/G190A	B	HeLa
	K103N/L1001	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L1001	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A	B	HeLa
	V106A/Y181C	B	HeLa
	V1081	A	HeLa
	V1081/Y181C	B	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
	Y188C	A	HeLa
79	HIV-1	A	MT4
	HIV-2	D	MT4
	NEV-R	A	MT4
	K103N	A	HeLa
	K103N/Y181C	A	HeLa
103	HIV-1	B	MT4
	NEV-R	C	MT4
	K103N	B	HeLa
120	HIV-1	B	MT4
	NEV-R	B	MT4
	K103N	B	HeLa
	K103N/Y181C	C	HeLa
	WTRVA	B	HeLa
	Y181C	B	HeLa

122	HIV-1	A	MT4
	NEV-R	B	MT4
	K103N	B	HeLa
	K103N/Y181C	D	HeLa
	WTRVA	B	HeLa
	Y181C	C	HeLa
239	HIV-1	A	MT4
	NEV-R	A	MT4
	E138K	A	HeLa
	G190A	A	HeLa
	G190E	A	HeLa
	K101E	A	HeLa
	K103N	A	HeLa
	K103N/G190A	B	HeLa
	K103N/L1001	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	B	HeLa
	L1001	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A	B	HeLa
	V106A/Y181C	C	HeLa
	V1061	A	HeLa
	V1061/Y181C	A	HeLa
	V1081	A	HeLa
	V1081/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
	Y188C	A	HeLa
257	HIV-1	A	MT4
	NEV-R	A	MT4
	E138K	A	HeLa
	G190A	A	HeLa
	G190E	A	HeLa
	K101E	A	HeLa
	K103N	A	HeLa
	K103N/G190A	B	HeLa
	K103N/L1001	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L1001	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A	B	HeLa
	V106A/Y181C	B	HeLa
	V1061	A	HeLa
	V1061/Y181C	B	HeLa
	V1081	A	HeLa
	V1081/Y181C	A	HeLa

	WTRVA	A	HeLa
	Y181C	A	HeLa
	Y188C	A	HeLa
338	HIV-1	A	MT4
	NEV-R	B	MT4
	K103N	B	HeLa
	K103N/Y181C	C	HeLa
	WTRVA	A	HeLa
	Y181C	B	HeLa
387	HIV-1	A	MT4
	NEV-R	B	MT4
	K103N	A	HeLa
	K103N/Y181C	B	HeLa
	WTRVA	A	HeLa
	Y181C	B	HeLa
435	HIV-1	A	MT4
	NEV-R	B	MT4
	K103N	A	HeLa
	K103N/Y181C	C	HeLa
	WTRVA	A	HeLa
	Y181C	B	HeLa
448	HIV-1	A	MT4
	HIV-2	D	MT4
	NEV-R	A	MT4
	E138K	A	HeLa
	G190A	A	HeLa
	G190E	A	HeLa
	K101E	A	HeLa
	K103N	A	HeLa
	K103N/G190A	B	HeLa
	K103N/L1001	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	B	HeLa
	L1001	A	HeLa
	P225H	A	HeLa
	P236L	B	HeLa
	V106A	B	HeLa
	V106A/Y181C	B	HeLa
	V1061	A	HeLa
	V1061/Y181C	B	HeLa
	V1081	A	HeLa
	V1081/Y181C	A	HeLa
	Y181C	A	HeLa
	Y188C	A	HeLa
453	HIV-1	A	MT4
	NEV-R	A	MT4
	G190A	A	HeLa
	K101E	A	HeLa
	K103N	A	HeLa
	K103N/G190A	B	HeLa

	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L1001	A	HeLa
	P225H	A	HeLa
	P236L	B	HeLa
	V106A	C	HeLa
	V106A/Y181C	B	HeLa
	V1061	A	HeLa
	V1061/Y181C	B	HeLa
	V1081	C	HeLa
	V1081/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
	Y188C	A	HeLa
491	HIV-1	A	MT4
	NEV-R	A	MT4
	G190A	A	HeLa
	K103N	A	HeLa
	K103N/G190A	B	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L1001	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A/Y181C	A	HeLa
	V1061	A	HeLa
	V1061/Y181C	B	HeLa
	V1081	A	HeLa
	V1081/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
564	HIV-1	A	MT4
	NEV-R	A	MT4
	G190A	A	HeLa
	K103N	A	HeLa
	K103N/G190A	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L1001	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A/Y181C	A	HeLa
	V106I	A	HeLa
	V106I/Y181C	A	HeLa
	V1081/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
587	HIV-1	A	MT4
	NEV-R	A	MT4
	G190A	A	HeLa

	K103N	A	HeLa
	K103N/G190A	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V108I	A	HeLa
	K103N/Y181C	A	HeLa
	L100I	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A/Y181C	A	HeLa
	V106I	A	HeLa
	V106I/Y181C	B	HeLa
	V108I	A	HeLa
	V108I/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
475	HIV-1	A	MT4
	NEV-R	A	MT4
	G190A	A	HeLa
	K103N	A	HeLa
	K103N/G190A	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L100I	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A/Y181C	A	HeLa
	V106I	A	HeLa
	V106I/Y181C	B	HeLa
	V108I	A	HeLa
	V108I/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
478	HIV-1	A	MT4
	NEV-R	A	MT4
	G190A	A	HeLa
	K103N	A	HeLa
	K103N/G190A	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L100I	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A/Y181C	A	HeLa
	V106I	A	HeLa
	V106I/Y181C	A	HeLa
	V108I	A	HeLa
	V108I/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
498	HIV-1	A	MT4
	NEV-R	A	MT4

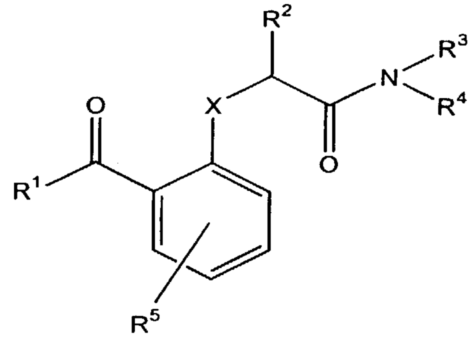
	G190A	A	HeLa
	K103N	A	HeLa
	K103N/G190A	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L100I	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A/Y181C	A	HeLa
	V106I	A	HeLa
	V106I/Y181C	B	HeLa
	V108I	A	HeLa
	V108I/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
593	HIV-1	A	MT4
	NEV-R	A	MT4
	G190A	A	HeLa
	K103N	A	HeLa
	K103N/G190A	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L100I	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A/Y181C	A	HeLa
	V106I	A	HeLa
	V106I/Y181C	B	HeLa
	V108I	A	HeLa
	V108I/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
483	HIV-1	B	MT4
	NEV-R	A	MT4
	K103N	C	HeLa
	V106A/Y181C	C	HeLa
	V106I	A	HeLa
	V106I/Y181C	B	HeLa
	WTRVA	B	HeLa
	Y181C	C	HeLa
637	HIV-1	A	MT4
	NEV-R	A	MT4
	G190A	A	HeLa
	K103N	A	HeLa
	K103N/G190A	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L100I	A	HeLa
	P225H	A	HeLa

	P236L	A	HeLa
	V106A/Y181C	A	HeLa
	V106I	A	HeLa
	V106I/Y181C	A	HeLa
	V108I/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
503	HIV-1	A	MT4
	NEV-R	A	MT4
	G190A	A	HeLa
	K103N	A	HeLa
	K103N/G190A	A	HeLa
	K103N/P225H	A	HeLa
	K103N/V1081	A	HeLa
	K103N/Y181C	A	HeLa
	L100I	A	HeLa
	P225H	A	HeLa
	P236L	A	HeLa
	V106A/Y181C	A	HeLa
	V106I	A	HeLa
	V106I/Y181C	A	HeLa
	V108I	A	HeLa
	V108I/Y181C	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
601	HIV-1	A	MT4
	NEV-R	A	MT4
	K103N	A	HeLa
	WTRVA	A	HeLa
	Y181C	A	HeLa
	V106A	A	HeLa

* A indicates an IC_{50} of 10nM or less
B indicates an IC_{50} between 11nM and 100nM
C indicates an IC_{50} between 101nM and 1,000nM
D indicates an IC_{50} between 1,000nM and 3,000nM

CLAIMS

1. A compound of formula (I



(I)

wherein:

X is C, O, or N;

R^1 is C_{1-8}alkyl; C_{3-6}cycloalkyl; C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$, $-S(O)_2NR^8R^9$, and $-SR^{10}N(R^{10})_2$; or C_{6-}

$_{14}$aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, -CF_3, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, -NO_2, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, -C(O)NH_2, -S(O)R^7, -$S(O)_2R^7$, -C(O)R^7, -$NS(O)_2R^7$, -$S(O)_2NR^8R^9$, -$S(O)_2NHR^{11}$, -$S(O)_2R^{11}$, -$S(O)_2NR^7COR^{11}$, -$S(O)_2NHCOR^{11}$, -$S(O)_2[COR^{11}]_n$ wherein n is 1, 2, or 3, -OR^{11} , -$OR^{11}OR^{11}$, -C(O)R^{11}, -C(O)NR^{11}, -C(O)OR^{11}, -NR^{11}, -NC(O)R^{11}, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and C(O)OR^{11}, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with -C(O)R^{11}; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, alkoxy, -$S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, and C_{1-8}alkyl; heterocycle optionally substituted with heterocycleC_{1-8}alkyl; or C_{6-14}aryl optionally substituted with alkoxy;

R^5 is hydrogen, halogen, C_{1-8}alkyl, -NO_2, -NH_2, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof, provided that

(a) when X is N; R^1 is C_{6-14}aryl substituted with halogen; R^2 and R^3 are hydrogen; R^5 is halogen; R^4 cannot be heterocycle substituted with C_{1-8}alkyl;

(b) when X is C; R^2 is hydrogen, halogen or C_{1-8}alkyl; R^3 is hydrogen; R^4 is C_{6-14}aryl substituted with halogen, hydroxy, or C_{1-8}alkyl; R^5 is hydrogen, halogen, C_{1-8}alkyl, or

alkoxy; then R^1 cannot be C_{1-8}alkyl, C_{3-6}cylcoalkyl, or C_{6-14}aryl substituted with halogen, C_{1-8}alkyl, alkoxy, or C_{6-14}arylC_{2-6}alkenyl; and

(c) when X is C; R^2 is hydrogen or alkyl, R^3 is hydrogen, R^4 is C_{6-14}aryl substituted with halogen, CN, C_{1-8}alkyl, or $-NO_2$; R^5 is hydrogen, $-NO_2$ or NH_2, then R^1 cannot be C_{10-14} aryl substituted with alkoxy.

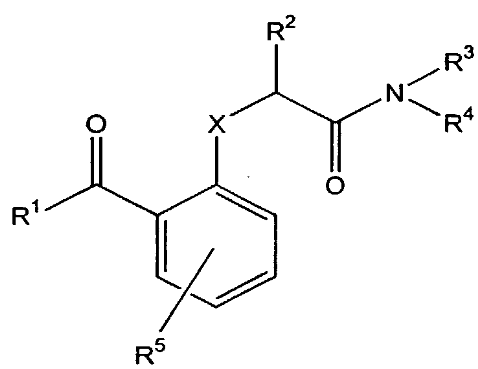
2. A compound of formula (I) according to claim 1 wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, -CN, $-SR^6$, $-S(O)_2R^6$; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, and C_{6-14}arylC_{1-8}alkyl; R^6 is C_{1-8}alkyl, optionally substituted with halogen; R^7 is C_{1-8} alkyl optionally substituted with one or more substituents selected from the group consisting of hydroxy; $-NH_2$, or heterocycle; R^2 is hydrogen; R^3 is hydrogen or C_{1-8} alkyl; R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$, $S(O)_2NR^8R^9$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, and heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl and heterocycleC_{1-8}alkyl; $R^8$and R^9 are the same or different and are selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cycloalkyl; R^{10} is C_{1-8}alkyl; R^{11} is C_{1-8}alkyl, optionally substituted with $-SO_2NR^8R^9$; and R^5 is halogen or $-NO_2$; or a pharmaceutically acceptable derivative thereof.

3. A compound of formula (I) according to claim 1 wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, and -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, $-NO_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-NS(O)_2R^7$, wherein R^7 is $-NH_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

4. A compound of formula (I) according to claim 1 wherein X is O; R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, CF_3, -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $S(O)_2NR^8R^9$, wherein $R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl.

5. A compound of formula (I) according to claim 1 wherein R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, and -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, $-NO_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-NS(O)_2R^7$, wherein R^7 is $-NH_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof provided that when X is C; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with halogen, CN, C_{1-8}alkyl, $-NO_2$; and R^5 is halogen, then R^1 cannot be C_{6-10}aryl substituted with alkoxy.

6. A compound of formula (IA)



(IA)

wherein:

X is C, O, or N;

R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-S(O)_2R^{11}$, $-S(O)_2NR^7COR^{11}$, $-S(O)_2NHCOR^{11}$, $-S(O)_2[COR^{11}]_n$ wherein n is 1, 2, or 3, $-OR^{11}$, $-OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, alkoxy, $-S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, and C_{1-8}alkyl; heterocycle optionally substituted with heterocycleC_{1-8}alkyl; or C_{6-14}aryl optionally substituted with alkoxy;

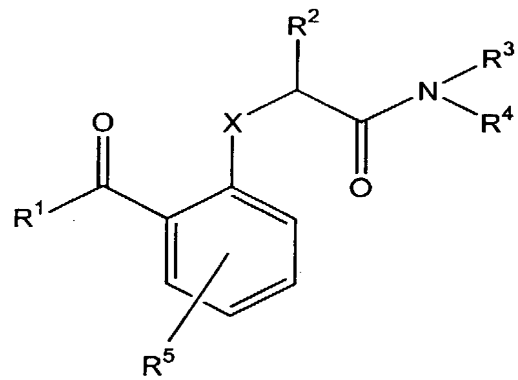
R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof provided that

a) when X is C; R^2 is hydrogen, halogen or C_{1-8}alkyl; R^3 is hydrogen; R^4 is C_{6-14}aryl substituted with halogen, hydroxy, or C_{1-8}alkyl; R^5 is hydrogen, halogen, C_{1-8}alkyl, or alkoxy; then R^1 cannot be C_{1-8}alkyl, C_{3-6}cycloalkyl, or C_{6-14}aryl substituted with halogen, C_{1-8}alkyl, or C_{6-14}arylC_{2-6}alkenyl; and

(b) when X is C; R^2 is hydrogen or alkyl; R^3 is hydrogen; R^4 is C_{6-14}aryl substituted with halogen, CN, alkyl, or $-NO_2$; R^5 is hydrogen, $-NO_2$, or NH_2, then R^1 cannot be C_{10-14} aryl substituted with alkoxy.

7. A compound of formula (IA) according to claim 6 wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, -CN, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, $-S(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, heterocycleC_{2-6}alkenyl, and heterocycle which may be optionally substituted with oxo; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

8. A compound of compounds of formula (IB)



(IB)

wherein:

X is C, O, or N;

R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$, $-SR^{10}N(R^{10})_2$, and $-S(O)_2NR^8R^9$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected

from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

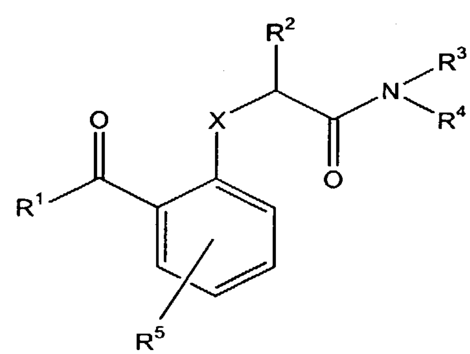
R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, hydroxy, halogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, alkoxy, $-S(O)_2NR^8R^9$, $NCONH_2$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, and C_{1-8}alkyl; heterocycle optionally substituted with heterocycleC_{1-8}alkyl; or C_{6-14}aryl optionally substituted with alkoxy;

R^5 is hydrogen, halogen,C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;
or a pharmaceutically acceptable derivative thereof provided that when X is N; R^1 is C_{6-14}aryl substituted with halogen; R^2 and R^3 are hydrogen; R^5 is halogen; R^4 cannot be heterocycle substituted with C_{1-8}alkyl.

9. A compound of formula (IB) according to claim 8 wherein X is O; R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, and -CN; R^2 is hydrogen; R^3 is hydrogen; R^4 is heterocycle; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

10. A compound of formula (IC)



(IC)

wherein:

X is C, O, or N;

R^1 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, halogen, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 is hydrogen;

R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-S(O)_2R^{11}$, $-S(O)_2NR^7COR^{11}$, $-S(O)_2NHCOR^{11}$, $-S(O)_2[COR^{11}]_n$ wherein n is 1, 2, or 3, $-OR^{11}$, $-OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

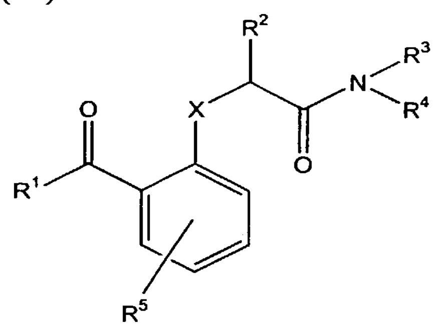
$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, alkoxy, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

11. A compound of formula (IC) according to claim 10 wherein X is O; R^1 is heterocycle, optionally substituted with -CN; R^2 and R^3 are hydrogen; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-OR^{11}$, and heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

12. A compound of formula (ID):



(ID)

wherein:

X is C, O, or N;

R^1 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, halogen, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$, $-S(O)_2NR^8R^9$, and $-SR^{10}N(R^{10})_2$;.or R^3 and R^4 together with the nitrogen atom to which they are attached form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{3-6}cycloalkyl, C_{1-8}alkyl optionally substituted with one or more substituents selected

from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl;

R^{10} is C_{1-8}alkyl;

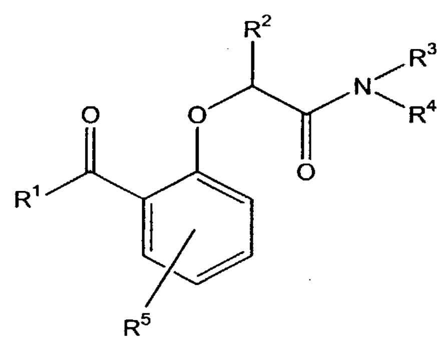
R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, and heterocycle optionally substituted with one or more substituents selected from the group consisting of oxo, and C_{1-8}alkyl;

R^5 is hydrogen, halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

13. A compound of formula (ID) according to claim 12 wherein X is O; R^1 is heterocycle; R^2 and R^3 are hydrogen; R^4 is heterocycle; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

14. A compound according to any of claims 1, 5, 6, 8, 10, or 12 wherein X is O.

15. A compound of formula (II):



(II)

wherein:

R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen, or C_{1-8}alkyl;

R^3 and R^4 form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$;

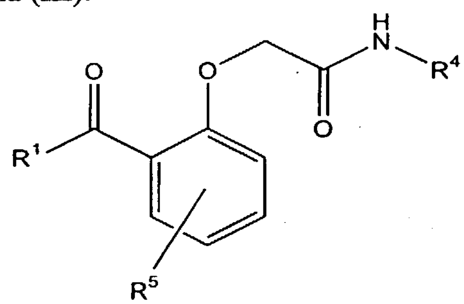
provided that when R^1 is unsubstituted C_{6-14}aryl, then R^3R^4 is substituted.

R^5 is hydrogen, halogen,C_{1-8}alkyl, $-NO_2$, $-NH_2$,C_{1-8}alkylamino, CF_3, or alkoxy;

or a pharmaceutically acceptable derivative thereof.

16. A compound of formula (II) according to claim 15 wherein R^1 is C_{6-14}aryl which is substituted with halogen; R^2 is hydrogen; R^3 and R^4 form a heterocycle which may be optionally substituted with C_{6-14}aryl, which may be optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl and $-NO_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

17. A compound of formula (III):



(III)

wherein:

R^1 is C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, $-OR^{11}$ and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-S(O)_2NHR^{11}$, $S(O)_2R^{11}$, $OR^{11}OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which

may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and -C(O)OR^{11}, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with -C(O)R^{11};

R^{8}and R^9 are independently selected from the group consisting of hydrogen; C_{3-6}cycloalkyl; C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, heterocycle, CN and C_{6-14}aryl optionally substituted with alkoxy, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, heterocycleC_{1-8}alkyl, C_{3-6}cycloalkylC_{1-8}alkyl, and C_{3-6}cycloalkyl; or –C(O)NH$_2$;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, alkoxy, -S(O)$_2$NR^{8}R^9, -NR^{8}R^9 and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen; halogen; C_{1-8}alkyl; -NO$_2$; -NH$_2$; C_{1-8}alkylamino; CF$_3$, or alkoxy;
or a pharmaceutically acceptable derivative thereof,
provided that:

(a) when R^4 is C_{6-14}aryl substituted with OR^{11} wherein R^{11} is NR^{8}R^9 wherein R^8 and R^9 are C_{1-8}alkyl, and R^1 is C_{6-14}aryl, then R^1 cannot be substituted in the para position, and

(b) R^1 and R^4 cannot both be unsubstituted.

18. A compound of formula (III) according to claim 17 wherein R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, -CF$_3$, C_{1-8}alkyl, -CN, -SR^6, -S(O)$_2$R^6; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, and C_{6-14}arylC_{1-8}alkyl; R^6 is C_{1-8}alkyl, optionally substituted with halogen; R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, -NH$_2$, or heterocycle; R^4 is heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, halogen, C_{1-8}alkyl, -OR^{11} and -SR^{10}N(R^{10})$_2$; or

C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, $-C(O)NH_2$, $-S(O)_2R^7$, -$S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; $R^8$and R^9 are the same or different and are selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cycloalkyl; R^{10} is C_{1-8}alkyl; R^{11} is C_{1-8}alkyl, optionally substituted with $-S(O)_2NR^8R^9$; and R^5 is halogen or $-NO_2$; or a pharmaceutically acceptable derivative thereof.

19. A compound of formula (III) according to claim 17 wherein R^1 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, and -CN; R^4 is C_{6-14}aryl substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -CN, $-NO_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-NS(O)_2R^7$, wherein R^7 is $-NH_2$; and R^5 is halogen; or a pharmaceutically acceptable derivative thereof.

20. A compound according to any of claims 1, 3, 4, 5, 6, 7, 17, 18, or 19 wherein

R^1 is phenyl which is substituted in the *meta* position with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, alkoxy, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, -$S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl, and heterocycle;

R^2 is hydrogen;

R^3 is hydrogen;

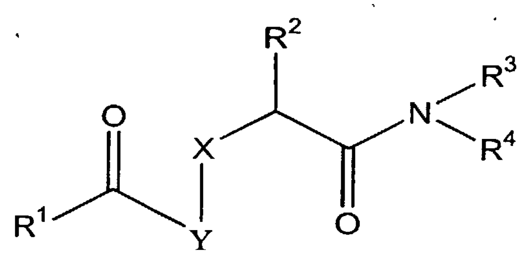
R^4 is phenyl substituted in the *ortho* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, or C_{1-8}alkyl and substituted at the *para* position with a substituent selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NS(O)_2R^7$, $-S(O)_2NR^8R^9$, $-S(O)_2NHR^{11}$, $-SO_2R^{11}$, $-OR^{11}$

, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$;

R^5 is a substituent in the *para* position relative to X and is selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-S(O)_2NR^8R^9$, $-NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl; or a pharmaceutically acceptable derivative thereof.

21. A compound of formula (IV)



(IV)

wherein:

X is C, O, or N;

Y is heterocycle optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, $-CF_3$, or alkoxy;

R^1 is C_{1-8}alkyl; C_{3-6}cycloalkyl; C_{6-14}aryl which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-CF_3$, C_{1-8}alkyl, C_{1-8}alkylamino, C_{3-6}cycloalkylC_{2-6}alkenyl, C_{6-14}arylC_{2-6}alkenyl, -CN, $-NO_2$, $-NH_2$, $-SR^6$, $-S(O)_2R^6$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, C_{2-6}alkenyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, and heterocycle, and C_{2-6}alkynyl which may be optionally substituted with a substituent selected from the group consisting of hydroxy, halogen, aryl, C_{3-}

${}_6$cycloalkyl, and heterocycle; or heterocycle, optionally substituted with one or more substituents selected from the group consisting of C_{1-8}alkyl, -CN, C_{6-14}arylC_{1-8}alkyl and heterocycle;

R^6 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, aryl, and heterocycle;

R^7 is C_{1-8} alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, aryl, C_{3-6}cycloalkyl and heterocycle; $-NH_2$; or heterocycle;

R^2 is hydrogen, halogen,or C_{1-8}alkyl;

R^3 and R^4 are independently hydrogen; hydroxy; heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo, hydroxy, hydroxyC_{1-8}alkyl, halogen, C_{1-8}alkyl, OR^{11} and $-SR^{10}N(R^{10})_2$; or C_{6-14}aryl substituted with one or more substituents selected from the group consisting of hydroxy, halogen, $-CF_3$, C_{1-8}alkyl, hydroxyC_{1-8}alkyl, -CN, $-NO_2$, C_{1-8}alkylamino, heterocycleC_{1-8}alkyl, $-C(O)NH_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-C(O)R^7$, $-NSO_2R^7$, $-S(O)_2NR^8R^9$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)NR^{11}$, $-C(O)OR^{11}$, $-NR^{11}$, $-NC(O)R^{11}$, heterocycleC_{2-6}alkenyl, heterocycle which may be optionally substituted with one or more substituents selected from the group consisting of oxo, C_{1-8}alkyl, and $C(O)OR^{11}$, and C_{1-8}alkyl which may be optionally substituted with one or more substituents selected from the group consisting of -CN and heterocycle, optionally substituted with $-C(O)R^{11}$; provided that R^3 and R^4 cannot both be hydrogen or hydroxy;

$R^8$and R^9 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8} alkylamino, C_{1-8}alkylheterocycle, heterocycle, and C_{3-6}cycloalkyl;

R^{10} is C_{1-8}alkyl;

R^{11} is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydrogen, C_{1-8}alkyl, $-SO_2NR^8R^9$, and heterocycle, optionally substituted with one or more substituents selected from the group consisting of oxo and C_{1-8}alkyl;

R^5 is hydrogen, halogen,C_{1-8}alkyl, $-NO_2$, $-NH_2$, C_{1-8}alkylamino, CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

22. A compound of formula (IV) according to claim 21 wherein Y is a heterocycle substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -NO_2, -NH_2, C_{1-8}alkylamino, -CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof. More preferred compounds of formula (IV) are compounds wherein X is O. Most preferred compounds of formula (IV) are those wherein X is O and Y is a heterocycle substituted with one or more substituents selected from the group consisting of halogen, C_{1-8}alkyl, -NO_2, -NH_2, C_{1-8}alkylamino, -CF_3, or alkoxy; or a pharmaceutically acceptable derivative thereof.

23. A compound selected from the group consisting of:

2-[2-(1-benzothiophen-2-ylcarbonyl)-4-chlorophenoxy]-N-phenylacetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1H-imidazol-1-yl)phenyl]acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1H-1,2,4-triazol-1-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(4-morpholinyl)phenyl]acetamide;

N-[4-(aminosulfonyl)phenyl]-2-(2-benzoyl-4-chlorophenoxy)acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[(1,3-thiazol-2-ylamino)sulfonyl]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(4-methyl-1-piperazinyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(hydroxymethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[(methylamino)sulfonyl]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1,1-dioxo-1lambda~6~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(4-morpholinyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[3-(dimethylamino)propoxy]-2-methylphenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(1-hydroxyethyl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-5-yl)acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(4-morpholinyl)propoxy]phenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{4-[3-(1H-imidazol-1-yl)propoxy]-2-methylphenyl}acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-(1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-{2-methyl-4-[3-(4-morpholinyl)propoxy]phenyl}acetamide;

2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-{2-methyl-4-[3-(1-oxo-1lambda~4~,4-thiazinan-4-yl)propoxy]phenyl}acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(2-benzoyl-4-chlorophenoxy)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(2-thienylcarbonyl)phenoxy]acetamide;

2-[2-(1-benzofuran-2-ylcarbonyl)-4-chlorophenoxy]-N-phenylacetamide

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-phenylacetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(2-furoyl)phenoxy]acetamide;

2-[4-chloro-2-(2-furoyl)phenoxy]-N-(1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3-furoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-[4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-thienylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-{4-chloro-2-[(1-methyl-1H-pyrrol-2-yl)carbonyl]phenoxy}-N-phenylacetamide;

2-(4-chloro-2-{[5-(2-pyridinyl)-2-thienyl]carbonyl}phenoxy)-N-phenylacetamide;

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-(1H-indazol-5-yl)acetamide;

2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-pyridinylcarbonyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(2-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(4-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[2-(2-bromobenzoyl)-4-chlorophenoxy]acetamide;

2-{4-chloro-2-[(5-methyl-3-isoxazolyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chlorobenzoyl)phenoxy]acetamide;

2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(4-cyano-2-thienyl)carbonyl]phenoxy}acetamide;

2-{4-chloro-2-[3-(trifluoromethyl)benzoyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[2-(3-bromobenzoyl)-4-chlorophenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[2-(3-bromobenzoyl)-4-chlorophenoxy]acetamide;

2-[4-chloro-2-(3-methylbenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-pyridinylcarbonyl)phenoxy]acetamide;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(1-methyl-1H-imidazol-2-yl)carbonyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(1,3-thiazol-2-ylcarbonyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-{2-methyl-4-[3-(1-pyrrolidinyl)propoxy]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide

N-(1,3-benzothiazol-6-yl)-2-(2-benzoyl-4-chlorophenoxy)acetamide

2-(4-chloro-2-{3-[(trifluoromethyl)sulfanyl]benzoyl}phenoxy)-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide

2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-[2-methyl-4-(1-oxo-1lambda~4~,4-thiazinan-4-yl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

N-(1,3-benzothiazol-6-yl)-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-(2-methyl-1,3-benzothiazol-5-yl)acetamide

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(4-chloro-2-{3-[(trifluoromethyl)sulfanyl]benzoyl}phenoxy)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]acetamide;

2-(2-benzoyl-4-chlorophenoxy)-N-[4-(methylsulfonyl)phenyl]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-(2-cyclopentylethynyl)benzoyl]phenoxy}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-(2-phenylethynyl)benzoyl]phenoxy}acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-indazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

N-(1,2-benzisothiazol-5-yl)-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-1-(2,3-dihydro-1H-indol-1-yl)-1-ethanone;

2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

2-[4-chloro-2-(3-ethynylbenzoyl)phenoxy]-N-[2-methyl-4-(methylsulfonyl)phenyl]acetamide;

N-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]acetamide;

2-{2-[3,5-bis(trifluoromethyl)benzoyl]-4-chlorophenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{2-[(5-bromo-3-pyridinyl)carbonyl]-4-chlorophenoxy}-N-(5-methyl-1H-benzimidazol-6-yl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(6-methyl-1,3-benzothiazol-5-yl)acetamide;

N-{4-[3-(aminosulfonyl)propoxy]-2-methylphenyl}-2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-(4-chloro-2-{3-[(trifluoromethyl)sulfonyl]benzoyl}phenoxy)acetamide;

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[4-(1,3-thiazol-2-yl)phenyl]acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-[4-(1,3-oxazol-2-yl)phenyl]acetamide

2-[4-chloro-2-(3,5-difluorobenzoyl)phenoxy]-N-{4-[(3-hydroxypropyl)sulfonyl]-2-methylphenyl}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(2-methyl-4-{3-[(methylamino)sulfonyl]propoxy}phenyl)acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-(4-{3-[(dimethylamino)sulfonyl]propoxy}-2-methylphenyl)acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{2-[(5-bromo-3-pyridinyl)carbonyl]-4-chlorophenoxy}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-{4-[3-(1H-imidazol-1-yl)propoxy]-2-methylphenyl}acetamide;

2-{4-chloro-2-[3-fluoro-5-(trifluoromethyl)benzoyl]phenoxy}-N-{2-methyl-4-[(E)-4-(1-pyrrolidinyl)-1-butenyl]phenyl}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[6-(aminosulfonyl)-4-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dimethylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-ethylbenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]-*N*-{4-[3-(2,5-dihydro-1*H*-pyrrol-1-yl)propoxy]-2-methylphenyl}acetamide hydrochloride;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(6-cyano-2-pyridinyl)carbonyl]phenoxy}acetamide;

N-[6-(aminosulfonyl)-2-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dicyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[3-cyano-5-(trifluoromethyl)benzoyl]phenoxy}acetamide;

and pharmaceutically acceptable derivatives thereof.

24. A compound selected from the group consisting of compound number 7, 32, 33, 36, 38, 44, 45, 49, 51, 52, 61, 65, 66, 71, 75, 76, 111, 112, 115, 118, 119, 128, 129, 171, 172, 191, 192, 199, 200, 206, 207, 224, 225, 232, 233, 235, 236, 246, 247, 253, 254, 255, 256, 259, 260, 261, 262, 264, 265, 267, 268, 288, 289, 290, 409, 412, 428, 430, 431, 433, 491, 564, 587, 475, 478, 498, 593, 483, 637, 503, 601, 658 and pharmaceutically acceptable derivatives thereof.

25. A compound selected from the group consisting of:
N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-fluoro-5-(trifluoromethyl)benzoyl]acetamide;

N-{4-[3-(aminosulfonyl)propoxy] -2-methylphenyl}-2-{4-chloro-2-[3-fluoro-5-(trifluomethyl)benzoyl]phenoxy}acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-fluorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[6-(aminosulfonyl)-4-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-cyanobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dimethylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-cyano-5-ethylbenzoyl)phenoxy]acetamide;

2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]-N-{4-[3-(2,5-dihydro-1H-pyrrol-1-yl)propoxy]-2-methylphenyl}acetamide hydrochloride;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3-chloro-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dichlorobenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-{4-chloro-2-[(6-cyano-2-pyridinyl)carbonyl]phenoxy}acetamide;

N-[6-(aminosulfonyl)-2-methyl-3-pyridinyl]-2-[4-chloro-2-(3-cyano-5-methylbenzoyl)phenoxy]acetamide;

N-[4-(aminosulfonyl)-2-methylphenyl]-2-[4-chloro-2-(3,5-dicyanobenzoyl)phenoxy]acetamide;

and pharmaceutically acceptable derivatives thereof.

26. A compound according to any of claims 1, 3, 4, 5, 6, 7, 17, 18, or 19 wherein R^1 is C_{6-14} aryl substituted in the meta position, particularly with halogen and wherein R^3 is hydrogen and R^4 is C_{6-14}aryl substituted with C_{1-8}alkyl, in particular methyl.

27. A method of treatment of a viral infection in a mammal comprising administering to said mammal an antivirally effective amount of a compound according to any of claims 1 to 26.

28. The method according to claim 27 wherein the viral infection is an HIV infection.

29. A method of inhibiting HIV reverse transcrptase comprising administering to a mammal an effective amount of a compound according to any of claims 1 to 26.

30. A method of preventing HIV infection, or of treating HIV infection, comprising administering to a mammal an effective amount of a compound according to any of claims 1 to 26.

31. Use of a compound according to any of claims 1 to 26 in the manufacture of a medicament for the treatment of an HIV infection.

32. Use of a compound according to any of claims 1 to 26 in the treatment or prophylaxis of a viral infection.

33. The use according to claim 32 wherein the viral infection is an HIV infection.

34. A pharmaceutical composition comprising an effective amount of a compound according to any of claims 1 to 26 together with a pharmaceutically acceptable carrier.

35. A pharmaceutical composition according to claim 34 in the form of a tablet or capsule.

36. A pharmaceutical composition according to claim 34 in the form of a liquid.

37. A compound as claimed in claims 1 to 26 for use as a medicament.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(81) **Designated States** *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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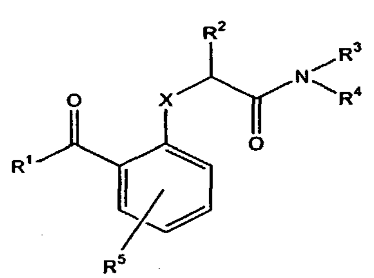
(54) **Title:** BENZOPHENONES AS INHIBITORS OF REVERSE TRANSCRIPTASE



(I)

(57) **Abstract:** The present invention includes benzophenone compounds (I) which are useful in the treatment of HIV infections.

WO 01/17982 A1

COMBINED DECLARATION FOR UTILITY OR DES. N PATENT APPLICATION WITH POWER OF ATTORNEY	ATTORNEY'S DOCKET PU3517USW
	First Names Inventor: Clarence Webster ANDREWS
( ) Declaration submitted with initial filing or	***Complete if known:*** App No.:
( )Declaration submitted after initial filing (surcharge required 37CFR1.16(e))	Filing Date
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Application Number **PCT/EP00/08487** filed and was amended on (MM/DD/YYYY) ________________(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

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PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

Prior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY))	PRIORITY CLAIMED
1 9920872.0	GB	09/04/1999	X
2.			
3.			
4.			
5.			

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U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one) PATENTED	PENDING	ABANDONED

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Karen L. PRUS
919-483-2192

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2	FULL NAME OF INVENTOR	FAMILY NAME ANDREWS	FIRST GIVEN NAME Clarence	SECOND GIVEN NAME/INITIAL Webster, III
	INVENTOR'S SIGNATURE	Signature		Date:
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2	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY Durham	STATE & ZIP CODE/COUNTRY North Carolina 27709, US
2	FULL NAME OF INVENTOR	FAMILY NAME FREEMAN	FIRST GIVEN NAME George	SECOND GIVEN NAME/INITIAL Andrew
	INVENTOR'S SIGNATURE	Signature		Date:
0	RESIDENCE & CITIZENSHIP	CITY Durham	STATE OR FOREIGN COUNTRY US	COUNTRY OF CITIZENSHIP US
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY Durham	STATE & ZIP CODE/COUNTRY North Carolina 27709, US
2	FULL NAME OF INVENTOR	FAMILY NAME ROMINES	FIRST GIVEN NAME Karen	SECOND GIVEN NAME/INITIAL Rene
	INVENTOR'S SIGNATURE	Signature		Date:
0	RESIDENCE & CITIZENSHIP	CITY Durham	STATE OR FOREIGN COUNTRY US	COUNTRY OF CITIZENSHIP US
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2	FULL NAME OF INVENTOR	FAMILY NAME TIDWELL	FIRST GIVEN NAME Jeffrey	SECOND GIVEN NAME/INITIAL H.
	INVENTOR'S SIGNATURE	Signature		Date:
0	RESIDENCE & CITIZENSHIP	CITY Durham	STATE OR FOREIGN COUNTRY US	COUNTRY OF CITIZENSHIP US
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY Durham	STATE & ZIP CODE/COUNTRY North Carolina 27709, US
2	FULL NAME OF INVENTOR	FAMILY NAME PIANETTI	FIRST GIVEN NAME ~~Pascal~~	SECOND GIVEN NAME/INITIAL Maurice, Charles
	INVENTOR'S SIGNATURE	Signature X		Date: X 22/08/08
0	RESIDENCE & CITIZENSHIP	CITY Les Ulis	STATE OR FOREIGN COUNTRY FR	COUNTRY OF CITIZENSHIP FR
6	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY Durham	STATE & ZIP CODE/COUNTRY North Carolina 27709, US

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY	ATTORNEY'S DOCKET PU3517USW
	First Names Inventor: Clarence Webster ANDREWS
( ) Declaration submitted with initial filing or ( )Declaration submitted after initial filing (surcharge required 37CFR1.16(e))	*Complete if known*: App No.:
	Filing Date
	Group Art Unit:

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

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the specification of which (check only one item below):

[ ]is attached hereto.
OR
[x] was filed on **31 August 2000** as United States application Serial No. ______________ or PCT International

Application Number **PCT/EP00/08487** filed and was amended on (MM/DD/YYYY) __________________(if applicable)

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1 9920872.0	GB	09/04/1999	X
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3.			
4.			
5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)	
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DECLARATION FOR 371 APPLICATION 070084 .030702

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PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one): PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith. (List name and registration number)

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919-483-2192

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2	FULL NAME OF INVENTOR	FAMILY NAME: ANDREWS	FIRST GIVEN NAME: Clarence	SECOND GIVEN NAME/INITIAL: Webster, III
	INVENTOR'S SIGNATURE	Signature: Clarence Webster Andrews Jr		Date: 3/1/02
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1	POST OFFICE ADDRESS	POST OFFICE ADDRESS: GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY: Durham	STATE & ZIP CODE/COUNTRY: North Carolina 27709, US NC
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	INVENTOR'S SIGNATURE	Signature: Joseph Chan		Date: 3/1/2002
0	RESIDENCE & CITIZENSHIP	CITY: Durham	STATE OR FOREIGN COUNTRY: US	COUNTRY OF CITIZENSHIP: US
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2	FULL NAME OF INVENTOR	FAMILY NAME: FREEMAN	FIRST GIVEN NAME: George	SECOND GIVEN NAME/INITIAL: Andrew
	INVENTOR'S SIGNATURE	Signature: George A. Freeman		Date: 3/1/02
0	RESIDENCE & CITIZENSHIP	CITY: Durham	STATE OR FOREIGN COUNTRY: US	COUNTRY OF CITIZENSHIP: US
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	INVENTOR'S SIGNATURE	Signature: Karen R Romines		Date: 1 March 2002
0	RESIDENCE & CITIZENSHIP	CITY: Durham	STATE OR FOREIGN COUNTRY: US	COUNTRY OF CITIZENSHIP: US
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ATTORNEY'S DOCKET NUMBER
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2 5 0 5	FULL NAME OF INVENTOR	FAMILY NAME TIDWELL	FIRST GIVEN NAME Jeffrey	SECOND GIVEN NAME/INITIAL H.
	INVENTOR'S SIGNATURE	Signature Jeff H Tidwell		Date: 02/20/2002
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	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY Durham	STATE & ZIP CODE/COUNTRY North Carolina 27709, US
2 6 0 6	FULL NAME OF INVENTOR	FAMILY NAME PIANETTI	FIRST GIVEN NAME Pascal	SECOND GIVEN NAME/INITIAL Maurice, Charles
	INVENTOR'S SIGNATURE	Signature		Date:
	RESIDENCE & CITIZENSHIP	CITY Les Ulis	STATE OR FOREIGN COUNTRY FR	COUNTRY OF CITIZENSHIP FR
	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	CITY Durham	STATE & ZIP CODE/COUNTRY North Carolina 27709, US